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Claudia Lunghi

Early cross-modal interactions and adult human visual cortical plasticity revealed by binocular rivalry

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Abstract

When two incompatible images are contemporaneously displayed to homologous portions of the two retinae normal binocular fusion fails, and conscious perception continuously oscillates between the two alternatives despite the constant retinal stimulation. This unique form of bistable visual perception is called *binocular rivalry*, and is a peculiar visual phenomenon that engages competition between monocular signals and neural representations of the two images at different levels of visual processing, from LGN to object-selective infero-temporal cerebral areas. Here we present several experiments in which we have used binocular rivalry as a tool to investigate different aspects of visual and multisensory perception.

In the first set of studies we demosntrated that touch specifically interacts with vision during binocular rivalry and that the interaction likely occurs at early stages of visual processing, probably V1 or V2. We found in fact that touching an engraved grating interfered with the dynamics of binocular rivalry both by prolonging dominance and by curtailing suppression of the congruent visual stimulus (parallel grating). We further demonstrated that the interaction between vision and touch during binocular rivalry was tightly tuned for matched visuo-haptic spatial frequencies and orientations. We finally showed that voluntary attention, action and proprioception do not play a leading role in mediating the interaction between vision and touch during rivalry, while spatial and temporal proximity between the visual and the haptic stimuli are necessary conditions for the interaction to occur.

In the second set of studies we demonstrated that human adult visual cortex retains an unexpected high degree of experience-dependent plasticity by showing that a brief period of monocular deprivation produced important perceptual consequences on the dynamics of binocular rivalry, causing the previously *deprived eye* to dominate rivalrous visual perception twice as long as the non-deprived eye. We also found that the effects of monocular deprivation were more long-lasting when visual stimuli modulated in chromaticity compared to luminance-modulated stimuli were tested, a result suggesting that chromatic vision retains a higher plastic potential. Finally, by showing that monocular deprivation also resulted in stimuli presented to the deprived eye appearing higher in contrast compared to stimuli presented to the non-deprived eye, we suggest that the perceptual advantage of the deprived eye during binocular rivalry measured after a short period of monocular deprivation reflects a compensatory homeostatic up-regulation of contrast gain control mechanisms that could be the first reaction of the visual system to the lack of information caused by deprivation.

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In conclusion, the work presented here demonstrates that, because of its unique characteristics binocular rivalry is a poverfool tool to investigate different aspects of visual perception and can be used to reveal unexpected properties of early visual cortex. We finally propose that, as suggested by preliminary results, binocular rivalry could be used as a non-invasive tool to monitor neuroplasticity during the recovery of vision in amblyopic children.

Chapter 1
General Introduction

1.1. What is Binocular Rivalry?

Our visual system is often faced with perceptual ambiguity and perceptual decisions need to be made in favour of one of the different interpretations to efficiently interact with the external world. According to the Bayesian theory of perception (for review see Knill & Pouget, 2004) the brain deals with perceptual uncertainty and ambiguity by representing sensory information in form of probability distributions. If different perceptual interpretations have the same likelihood and are mutually exclusive, the visual system cannot "decide" in favour of one or the other and visual perception continuously oscillates between the two alternatives. Most of the times *ambiguous figures* producing perceptual alternations (a behavior called *bistability*) are a consequence of unnatural visual stimulation often caused by a failure in depth perception derived by mapping a three-dimensional object into a flat surface. Bistable perception (Blake & Logothetis, 2002) is thought to reflect the competition between population of neurons encoding the two incompatible interpretations.

Ambiguous figures have been rousing the interest of visual scientists and artists. Figure 1.1.1 reports the most famous examples of bistable figures taking advantage of different forms of ambiguity: ambiguity in depth (the Necker cube, Necker, 1832, the Koffka cube, Koffka, 1935, and Schroeder's stairs), ambiguity in figure-ground segregation (Rubin's face-vase illusion, Rubin, 1915) and ambiguity between high-level interpretations of images (Boring's young girl/old woman figure, Boring, 1930 and Jastrow's rabbit/duck image, Jastrow, 1899). The lower panels of figure 1.1.1. report two examples of how ambiguous figures have been used by artists creating stunning pictorial effects.

Binocular rivalry is a particular type of perceptual bistability that is caused by a conflict between monocular images rather than between different interpretations of the same monocular image. When two incompatible visual stimuli are contemporaneously displayed on homologous portions of the two retinae the brain lapses into confusion, interpreting the two visual signals as arising from two different objects occupying the same spatio-temporal location in the external world. As a result, the two images do not merge into a coherent percept, but engage a strong competition for visual awareness with visual perception continuously alternating between the two rivalring visual stimuli (a diagram of the phenomenon is shown in Figure 1.1.3.).

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The systematic study of binocular rivalry was initiated by Sir Charles Wheatstone, who in 1838 invented a simple and smart instrument that allowed the contemporaneous presentation of different visual stimuli to the eyes (Wheatstone, 1838): the *mirror stereoscope* (Figure 1.1.2). After characterizing stereo-depth created using the mirror stereoscope, Wheatstone noted that something funny happened when dissimilar images were presented to the eyes (for example two different letters surrounded by a common circle to promote binocular fusion).

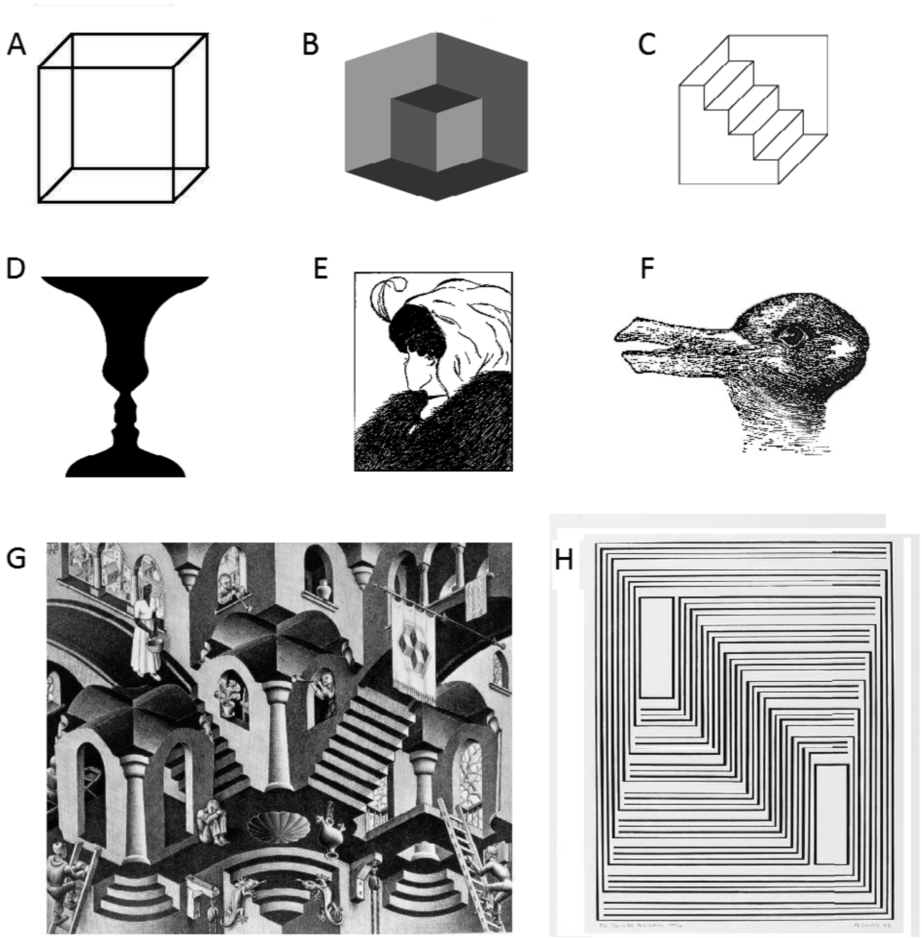


Figure 1.1.1. Examples of ambiguous figures leading to bistable perception.
Different types of well known ambiguous figures (Panels A-F) are reported: (A) the Necker cube (Necker, 1832), (B) the Koffka cube (Koffka, 1935) and (C) Shroeder's stair, for ambiguity in depth; (D) Rubin's vase/face illusion (Rubin, 1915) for ambiguity in figure-ground segregation; (E) Boring's old woman/young lady figure (Boring, 1930) and (F) Jastrow's rabbit/duck figure (Jastrow, 1899). The mutual exclusivity between different interpretations of each figure generates continuous perceptual alternations between the two views, a phenomenon known as *visual bistability*. Two examples of artworks using ambiguous figures to create visual illusions are reported: (G) M.C. Escher, *Convex and Concave, 1955* and (H) J. Albers, *To Monte Alban*, 1942. Ambiguous figures have been used in art since the roman empire.

At the beginning of the nineteenth century, Wheatstone described the characteristics of this new, unusual visual phenomenon capturing all the main features of binocular rivalry (comprising the most controversial characteristics of binocular rivalry that we will discuss in the following paragraphs, as they are still currently debated):

> “If *a* and *b* (fig. 25.) are each presented at the same time to a different eye, the common border will remain constant, while the letter within it will change alternately from that which would be perceived by the right eye alone to that which would be perceived by the left eye alone. At the moment of change the letter which has just been seen breaks into fragments, while fragments of the letter which is about to appear mingle with them, and are immediately after replaced by the entire letter. It does not appear to be in the power of the will to determine the appearance of either of the letters, but the duration of the appearance seems to depend on causes which are under our control: thus if the two pictures be equally illuminated, the alternations appear in general of equal duration; but if one picture be in ore illuminated than the other, that which is less so will be perceived during a shorter time. I have generally made this experiment with the apparatus, fig. 6. When complex pictures are employed in the stereoscope, various parts of them alternate differently.” (Wheatstone, 1838), p.383)

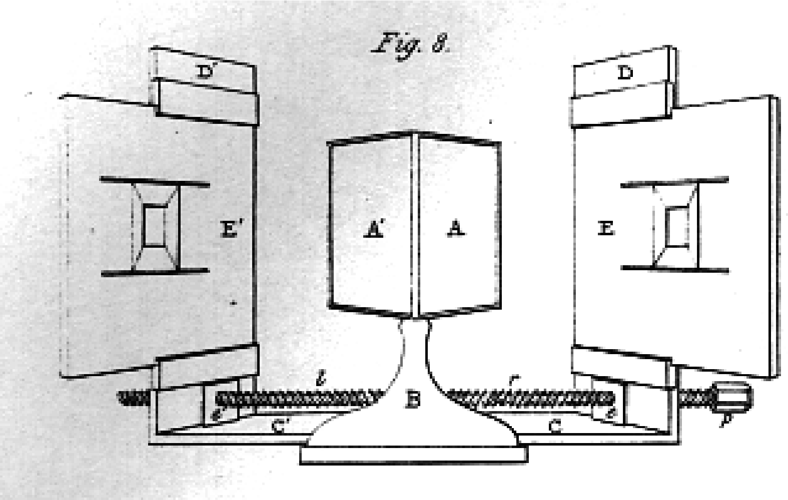


Figure 1.1.2. The mirror stereoscope invented by Sir Charles Wheatstone.
Adapted from (Wheatstone, 1838)

After the observations made by Wheatstone, binocular rivalry has attracted the attention of a growing number of visual scientists and is now one of the “hot topics” in visual research (D. H. Baker, 2010) because of the peculiar properties that make binocular rivalry a fascinating and unique phenomenon and an extraordinary tool to investigate different aspects of visual perception (Figure 1.1.4. shows a histogram of the number of publications per year regarding binocular rivalry over the past sixty years).

What is striking about binocular rivalry is that at any time one of the competing monocualr images, albeit present on the retina, is rendered invisible, a phenomenon known as *binocular rivalry suppression*. During binocular rivalry each of the two images, in fact, undergoes several phases of dominance and suppression with a peculiar dynamics that is linked to the relative strength of the visual signals associated with each image (Levelt, 1965). Dominance and suppression phases during binocular rivalry are thought to be independent processes (Blake & Logothetis, 2002) and show different sensitivities to external influences (e.g. attention, visual context, adaptation). Binocular rivalry suppression will be discussed later in a dedicated paragraph.

Because of the atypical dissociation between fluctuating visual conscious perception and constant physical stimulation, binocular rivalry has been expressively ascertained as one of the most interesting methods for investigating the neural correlates of visual awareness. The idea of taking advantage of bistable perception in general and binocular rivalry in particular to investigate at which stage of neural processing visual awareness (and consciousness) emerges has been influentially propounded in 1998 by Crick and Koch, whose paper "Consciousness and Neuroscience" (Crick & Koch, 1998) reviewed electrophysiological experiments on monkeys perceiving binocular rivalry (Leopold & Logothetis, 1996; Logothetis & Schall, 1989; Sheinberg & Logothetis, 1997) capturing the attention of a vast audience and giving rise to the "binocular rivalry explosion" (D. H. Baker, 2010) (Figure 1.1.3).

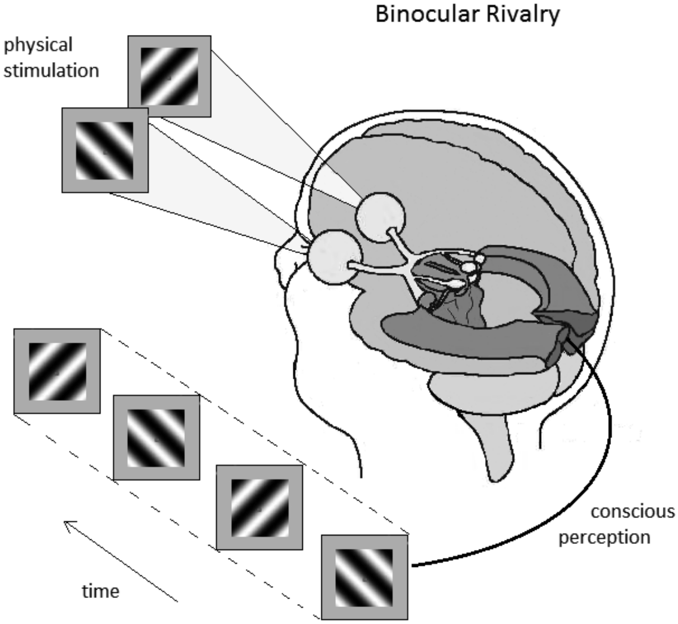


Figure 1.1.3. Binocular Rivalry
Diagram representing the phenomenon of binocular rivalry: when two unrelated images (for example orthogonal gratings) are contemporaneously presented to the eyes visual conscious perception alternates between the two images despite constant physical stimulation.

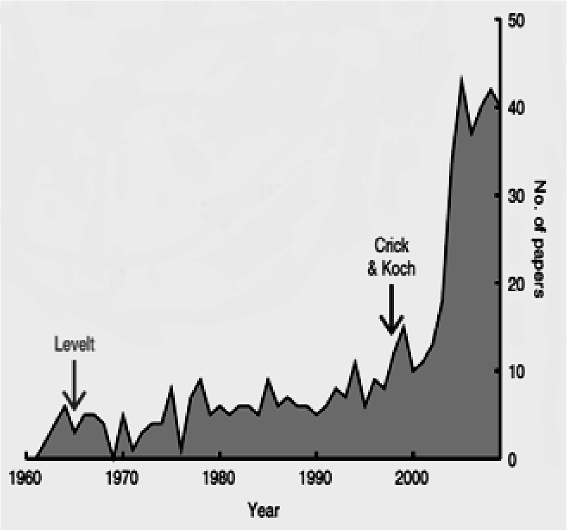


Figure 1.1.4. Number of publications on binocular rivalry (past 60 years). Adapted from (D. H. Baker, 2010)
Histogram of the number of papers indexed by PubMed on Binocular Rivalry by year. The arrows indicate the publication of the initial report by Levelt aand the publication of the influential paper on consciousness by Crick & Koch.

1.2. What rivals during binocular rivalry? Eye versus Stimulus Rivalry.

Binocular rivalry is a unique and complex visual phenomenon: the question about the neural correlates underlying binocular rivalry has generated a widespread debate and a lot of experimental evidence has been produced in favour of two major theories, one supporting the idea of binocular rivalry being generated at early stages of visual processing from the conflict between monocular representations of the competing stimuli (*eye rivalry*), the other supporting the idea of binocular rivalry being generated between high-level representations of the competing images processed at higher levels of visual analysis (*stimulus rivalry*).

The theory of eye-based rivalry has been formulated in the late 80s and considered binocular rivalry as being a local process, originating from the competition between neuronal populations representing corresponding regions of the two eyes, the population of neurons receiving the input from the dominant eye suppressing the corresponding neural population of the other eye. In this view, binocular rivalry is thought to emerge early in the visual system, where the neural populations representing the rivalring stimuli preserve the information about the eye-of-origin, so before binocular combination (Blake, 1989; Lehky, 1988). Consequently, according to this model, binocular rivalry derives from interocular competition at the thalamic level (LGN) and in the primary visual cortex, that is the last stage of visual analysis receiving direct inputs from monocular neurons (Hubel & Wiesel, 1977; Maunsell &

Van Essen, 1983). One of the main psychophysical evidence supporting eye-rivalry at that time was the *non-selectivity* of binocular rivalry suppression: during suppression phases of binocular rivalry, sensitivity markedly decreases, but this lack of sensitivity is generalized to all information presented to the suppressed eye and not limited to the features regarding the suppressed stimulus. Non-selectivity implies that suppression is acting on all stimulus features, say at a low-level, for a local portion of the eye (Blake & Fox, 1974c; Fox & Check, 1968; O'Shea & Crassini, 1981b; Wales & Fox, 1970; Zimba & Blake, 1983).

More recently, eye-rivalry has been supported by psychophysical evidence showing that eye-of-origin information is important for different aspects of binocular rivalry: dominance during binocular rivalry between complex images (faces) has been shown to spread from monocular regions (Arnold, James, & Roseboom, 2009), binocular rivalry has been shown to be sensitive to real-world occlusion constraints linked to monocular information (Shimojo & Nakayama, 1990), exogenous attention can be attracted during binocular rivalry by presenting a monocular cue (Ooi & He, 1999) and the dominant eye has been show to stabilize rivalrous perception in the initial seconds of dominance (Bartels & Logothetis, 2010). Further support to eye-based rivalry has been obtained by electrophysiological recordings showing strong interocular suppression in the primary visual cortex of cats during dichoptic stimulation (Sengpiel, Blakemore, Kind, & Harrad, 1994) and by neuroimaging studies showing awareness-related modulations of BOLD signal during binocular rivalry at early levels of visual processing: LGN (Haynes, Deichmann, & Rees, 2005; Wunderlich, Schneider, & Kastner, 2005) and monocular regions of primary visual cortex identified using the representation of the blind spot (Tong & Engel, 2001).

The theory contradicting eye-based models of binocular rivalry has been derived by two main experiments both published in 1996, one showing interocular grouping between rivalring visual stimuli (Kovacs, Papathomas, Yang, & Feher, 1996), the other demonstrating the survival of slow perceptual alternations despite the continuous interocular swapping of the two rivalring images (Logothetis, Leopold, & Sheinberg, 1996).

With a simple and smart paradigm, Kovacs et al (1996) tackled the question whether monocular representations or stimulus representations were engaged in binocular rivalry by presenting different patchwork images to the eyes each one being made of parts of two coherent images (i.e. a monkey and a jungle with a writing, Figure 1.2.1B). If binocular rivalry were the result of competition between monocular signals visual perception would be expected to oscillate between the two patchwork images, if instead rivalry resulted from the competition between coherent representations of complex images, perception would be expected to alternate between the monkey face and the writing (Kovacs, Papathomas, Yang, & Feher, 1996). To reduce the influence of semantic processing and isolate the role of pattern coherency in guiding binocular rivalry alternations, the authors focused on chromaticity as grouping attribute and presented pairs of visual stimuli made of patchwork colors (red and green over a yellow background, Figure 1.2.1D). Kovacs et al (1996) found that rivalry between uniform colors was perceived on 60% of trials, indicating interocular grouping between coherent elements during binocular rivalry. From this result the authors concluded that binocular rivalry occurred between stimulus representations, driven by pattern coherency rather than being only driven by monocular inhibitory interactions (Kovacs, Papathomas, Yang, & Feher, 1996).

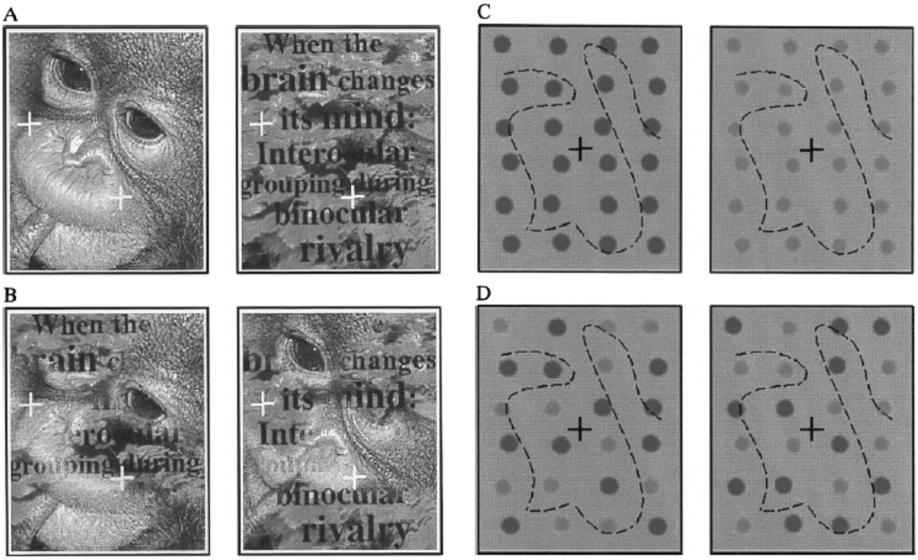


Figure 1.2.1. interocular grouping during binocular rivalry. Adapted from (Kovacs, Papathomas, Yang, & Feher, 1996)
Visual stimuli used by Kovacs et al to demonstrate the occurrence of interocular grouping during binocular rivalry, when patchworks of two coherent images are presented dichoptically, visual perception alternates between the two coherent patterns most of the time.

Inspired by this first result, several successive experiments have been performed demonstrating interocular grouping during binocular rivalry, including contour grouping ("association field", Alais, Lorenceau, Arrighi, & Cass, 2006), interocular grouping during different forms of rivalry (Pearson & Clifford, 2005b) and flicker-modulated grouping (Knapen, Paffen, Kanai, & van Ee, 2007; Silver & Logothetis, 2007). Support to the involvement of top-down feedbacks in regulating visual perception during binocular rivalry (being probably involved in mediating interocular grouping), has been also obtained by neuroimaging studies, demonstrating the activation of a fronto-parietal network (also implicated in spatial attention) of cortical areas during binocular rivalry (Lumer, Friston, & Rees, 1998).

The other strong evidence in favour of stimulus-based rivalry view was presented by Logothetis, Leopold and Sheinberg (1996) that introduced an interocular switching paradigm (IOS), in which orthogonal gratings flickering at a frequency 18 Hz were swapped between the eyes every 333 milliseconds (Figure 1.2.2.). If binocular rivalry was guided only by reciprocal inhibition between monocular representations, visual perception would alternate regularly following the interocular swapping rate (3 Hz). The authors found instead that, under these conditions, observers experienced the classic slow irregular alternations that characterize binocular rivalry, indicating that binocular rivalry also arises from competition between high level representations of the stimuli. The authors named this phenomenon *stimulus rivalry*, (Logothetis, Leopold, & Sheinberg, 1996).

The currently most common conceptualization of binocular rivalry is a hybrid model in which binocular rivalry is thought to take place at different levels of visual analysis, from different and interconnected neural events distributed over the visual hierarchy (Alais & Blake, 2005; Blake, 2001; Blake & Logothetis, 2002; Tong, Meng, & Blake, 2006; H. R. Wilson, 2003). Eye-based and stimulus-based rivalry have in fact been demonstrated to be different, but related phenomena, coexisting, rather than being exclusive. For example, Lee and Blake (1999) have shown that stimulus rivalry occurs only under specific, controlled conditions, and is confined to a limited range of spatial and temporal frequencies (Lee & Blake, 1999); a couple of years later Bonneh, Sagi and Karni (2001) have extended the specificity of stimulus rivalry to stimulus coherence, size and contrast (Bonneh, Sagi, & Karni, 2001).

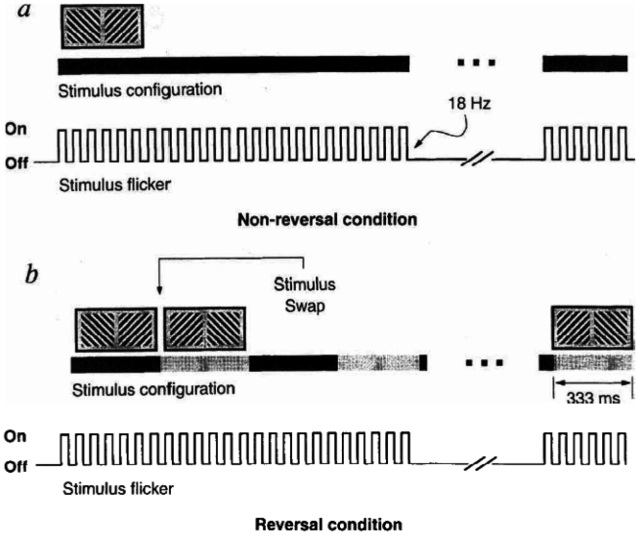


Figure 1.2.2. Interocular Switching Paradigm (IOS). Adapted from (Logothetis, Leopold, & Sheinberg, 1996).
Orthogonal gratings flickering at 18 Hz presented dichoptically are swapped between the eyes every 333 milliseconds.

Eye- and stimulus-rivalry have also been demonstrated to occur at different times during a dominance phase, eye-of-origin information playing a leading role in the initial stabilization of visual perception after a perceptual switch during binocular rivalry, stimulus configuration contributing importantly in the subsequent perceptual stability of the dominant image (regardless of the visual stimulus used, Bartels & Logothetis, 2010). This has been shown either by swapping the images between the eyes or by introducing brief blank periods disrupting stimulus coherency: dominance of a particular visual stimulus was interrupted when the interocular swap occurred early after a switch, but not by early blanks, while a few seconds after dominance stabilization, a switch was more likely to be caused by blank periods rather than eye-swaps (Bartels & Logothetis, 2010). Finally, a different contribution of the Magnocellular and Parvocellular pathways has been recently demonstrated for the two types of rivalry, eye rivalry being mostly driven by the Magnocellular pathway and stimulus rivalry being mostly driven by the Parvocellular pathway (Denison & Silver, 2012).

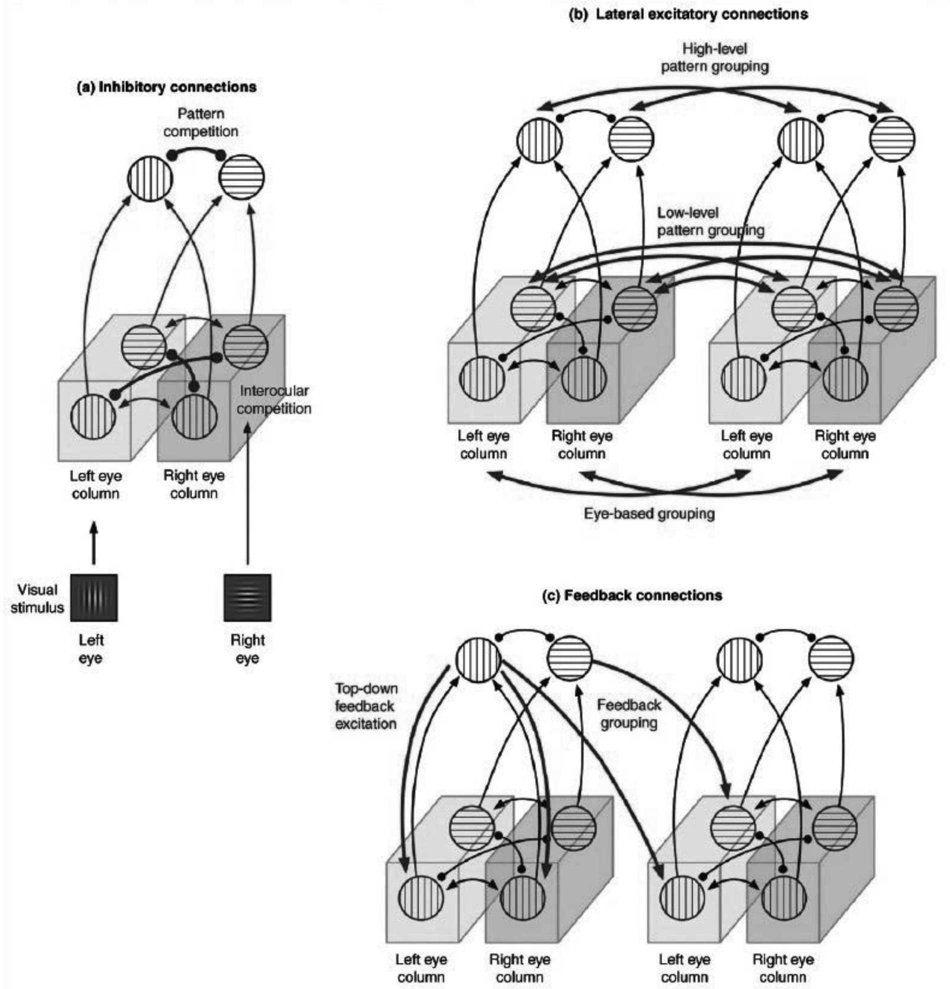


Figure 1.2.3. Hybrid Model of Binocular Rivalry. Adapted from (Tong, Meng, & Blake, 2006). The figure shows the three levels of interaction between visual neurons during rivalry: (a) the inhibitory connections between monocular neurons instigating rivalry; (b) Excitatory connections within low-level or high-level neurons promoting different types of grouping; (c) Feedback projections from high- to low-level areas, modulating neuronal activity at the monocular level.

Taken together, psychophysical evidence revealing the existence of two distinct but related types of rivalry, one eye-based, preserving information about the eye-of origin, the other stimulus-based, immune to interocular swaps and showing interocular grouping, electrophysiological recordings from monkey brain exhibiting a hierarchy of awareness-dependent fluctuations of neuronal activity and neuroimaging recordings in humans showing both early (LGN, V1) and higher level (inferotemporal cortex, fronto- parietal areas, attention network) modulations of the BOLD signal support the hybrid model that characterizes binocular rivalry as being a complex phenomenon recruiting a distributed network of visual activity. Visual competition during binocular rivalry starts early in the visual system, where it is mainly driven by interocular competition (i.e. reciprocal inhibition between monocular neural populations). Proceeding along the visual hierarchy, after binocular combination, competition goes on between neural populations representing visual stimuli configuration. Activity from these higher level areas can feed back into early areas to count for interocular grouping observed for patchwork monocular images, and frontal and parietal areas (neural network also engaged in spatial attention), modulates switching by feedbacks to the prior stages of processing, Figure 1.2.3, Tong, Meng, & Blake, 2006).

1.3. Binocular Rivalry dynamics.

One of the particular characteristics of binocular rivalry dynamics is the *unpredictability* of dominance phase durations. Perceptual oscillations during binocular rivalry, in fact, are not regular: periods of dominance of the visual stimulus presented to the right eye and that presented to the left eye do not follow a stable time constant and seem to be governed by a *stochastic mechanism* (Fox & J., 1967; Lehky, 1995; Levelt, 1966, , 1967). Dominance phase durations during binocular rivalry are independent: even considering the whole prior history of phase durations, the duration of the current dominant phase would be unpredictable.

Another feature of binocular rivalry is its *ineluctability*: once the conditions favourable to elicit binocular rivalry are created (i.e. when two images differing along one of diverse spatial and temporal dimensions are separately presented to the eyes) the observer cannot avoid experiencing perceptual alternations. Not only the induction, but also the continuation of binocular rivalry alternations is compulsory: the observer cannot hold indefinitely one of the two visual stimuli: no matter its relevance and meaning (Blake, 1988) or observer’s voluntary attention (Lack, 1978), the temporarily dominant image will always be supplanted by the previously suppressed image presented to the other eye.

Finally, binocular rivalry alternations are characterized by *mutual exclusivity*: one of the two rivalring images is perceived at a time only to be replaced by the previously suppressed image, in a winner-takes-it-all dynamics and the two visual stimuli are not perceived at the same time. Brief periods of “patchy rivalry” can nevertheless occur during transitions from dominance of one stimulus to dominance of the other. Perceptual switches during binocular rivalry are not immediate like a sequence of flashed photographs, but they reflect a travelling wave of neural activity (Lee, Blake, & Heeger, 2005) originating from a region of the visual stimulus and then spreading to the whole image in a wave-form way (Paffen, Naber, & Verstraten, 2008). These transitional waves are especially evident and slower when large visual stimuli are presented in central vision, suggesting that perceptual dominance during binocular rivalry is mediated by local cooperating neural populations that are organized according to retinotopic coordinates (Wilson, Blake, & Lee, 2001). Under optimal conditions (small, high-contrasted visual stimuli) however, periods of mixed perception do not normally exceed 10-15% of the total viewing time and are confined to transitions periods.

1.3.1. Phase duration distribution

As anticipated in the previous paragraph, binocular rivalry phase durations are unpredictable and stochastically organized. The distribution of phase durations shows a typical unimodal distribution with a positive asymmetrical shape skewed towards phase durations longer than the average, a type of distribution that is typical of stochastic phenomena. Phase duration distribution can be approximated either by a *gamma distribution* (Levelt, 1967) or a *log normal* distribution (Lehky, 1995). Switching rate during binocular rivalry and other forms of perceptual bistability is coherent for each observer, but shows a large inter-individual variation (Carter & Pettigrew, 2003). When averaging across observers, in fact, normalizing individual phase duration distributions to individual mean phase duration is a common and necessary procedure (Levelt, 1967). Interestingly, interindividual differences in switching rate during bistable visual perception have been shown to have a genetic component (52% of variability explained in monozygotic twins, Miller et al., 2010; Shannon, Patrick, Jiang, Bernat, & He, 2011) and to be linked to differences in brain structure and connectivity using magnetic resonance imagning (Genc, Bergmann, Singer, & Kohler, 2011; Genc et al., 2011; Kanai, Bahrami, & Rees, 2010; Kleinschmidt, Sterzer, & Rees, 2012).

In this paragraph we will focus on the *gamma distribution* because it is the most commonly used function to model phase duration distribution in binocular rivalry. An example of a gamma distribution of the form $g(x) = [\lambda^r x^{r-1}/\Gamma(r)]\exp(-\lambda x)$, where Γ is the *gamma function*, is shown in figure 1.3.1. The gamma distribution is characterized by two parameters: r is the shape parameter and λ is the scale parameter (we will come back to the meaning of the parameters in the next paragraph), the exponential distribution and the chi-squared distribution are two particular cases of the gamma distribution.

Even though the gamma-like shape of phase duration distributions has been considered an hallmark of binocular rivalry and bistable perception in general (Carter & Pettigrew, 2003; van Ee, 2005), and it has also been used as a validation for adequate binocular rivalry dynamics (Leopold & Logothetis, 1996, 1999; Logothetis, Leopold, & Sheinberg, 1996), some criticism on the application of gamma distribution for modelling binocular rivalry dynamics has been risen. For example, since the two parameters of the gamma distribution usually correlate or are even identical when binocular rivalry phase duration distributions are fitted by a gamma distribution function, the two parameters have been considered as redundant (De Marco, Penengo, & Trabucco, 1977; Mamassian & Goutcher, 2005) and so the gamma function.

In general, using phase duration distribution as only parameter to describe the dynamics of binocular rivalry is limiting, because it does not take into account the temporal succession of events during an extended period of binocular rivalry. Phase duration is an important factor because it is an index of the stability of bistable perception: short phases indicate periods of unstable perception in which switches occur rapidly, while longer phases indicate periods of more stable perception during which the alternation rate is slow. As we will detail in the next paragraphs, alternation rate is indicative of stimulus strength and can be also altered by internal factors as arousal and attention. Even though it is generally true that phase durations during binocular rivalry follow stochastic neural fluctuations, over an extended epoch of viewing periods of fast and slow alternations may occur (Mamassian & Goutcher, 2005) and such variations in alternation rate are not captured by phase duration distributions where phase durations are collapsed disregarding of their temporal order.

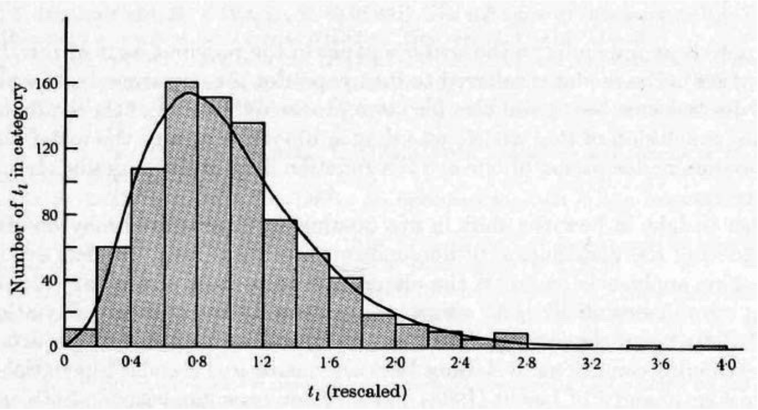


Figure 1.3.1. Binocular Rivalry Phase Duration Distribution. Adapted from (Levelt, 1967). The figure shows the histogram of phase durations of one eye fitted by a gamma distribution function of the form $g(x) = [\lambda^r x^{r-1}/\Gamma(r)]\exp(-\lambda x)$. Before plotting, phase durations have been normalized to the average phase durations of that eye. Normalization is a common procedure in binocular rivalry especially when averaging across observers because mean phase durations show a massive inter-individual variance.

In order to compensate for the incompleteness of phase duration distributions in describing the temporal dynamics of binocular rivalry, different methods of analysis have been proposed, for example, Mamassian & Goutcher (2005) have introduced the analysis of instantaneous probability as a dynamic method for characterizing visual perception during binocular rivalry. To improve the objectivity of the measurement of visual rivalrous perception they have also introduced a new recording method in which the observer is required to report visual perception every couple of second in correspondence of an acoustic signal (Mamassian & Goutcher, 2005). They have then computed the reversal probability separately for the two visual stimuli and the survival probability at each time bin during extended periods of observation obtaining "probability traces" describing the dynamics of binocular rivalry.

1.3.2. Stimulus strength and the dynamics of binocular rivalry

Despite the overall randomness underlying binocular rivalry dynamics, predominance of rivalring visual stimuli is dependent on the relative strength of the competing images. The dependence of phase duration on stimulus strength has been detailed for the first time by W.J. Levelt that in 1965 described how increasing "contour strength" of the stimulus presented to one eye increased the overall predominance (percentage of the total time of perceptual dominance over an extended period of viewing) of that stimulus (Levelt's first proposition, Levelt, 1965). The observation that the stronger rivalring stimulus dominates over the weaker one is not surprising and has been confirmed for different low-level characteristics of the visual stimuli: brightness (Fox & Rasche, 1969; I. T.

Kaplan & Metlay, 1964), contrast (Hollins, 1980; Whittle, 1965), contour density (Levelt, 1965), spatial frequency (Andrews & Purves, 1997; Fahle, 1982) and velocity (Blake, Yu, Lokey, & Norman, 1998; Wade, de Weert, & Swanston, 1984).

What happens if stimulus strength is varied symmetrically in both eyes? Levelt's third and fourth propositions address this issue, stating that increasing stimulus strength of both visual stimuli during binocular rivalry speeds up the switching rate (Levelt, 1966). As for the first one Levelt's third and fourth propositions have been generally accepted by the scientific audience and no objections have been risen against them. Levelt's second proposition is less intuitive and more problematic than the other three, stating that the overall predominance of the stronger stimulus is not explained by the stronger stimulus showing prolonged dominance durations, but is instead due to dominance durations of the weaker stimulus being curtailed. In short, increasing stimulus strength in one eye does not increase dominance of that eye, but rather decreases its suppression. As a consequence of Levelt's second proposition, counter-intuitively, changes in dominance duration of one eye depend on stimulus strength of the other eye. Regarding phase duration distributions, Levelt associated the scale parameter λ to the strength of the stimulus presented to the other eye, and therefore inversely correlated with dominance duration of that eye.

Even though Levelt's second proposition has been generally confirmed (Blake, 1977; Fox & Rasche, 1969; Logothetis, Leopold, & Sheinberg, 1996; Meng & Tong, 2004), some studies have demonstrated both diminished suppression and prolonged dominance durations of one of the rivalring stimuli after increasing its stimulus strength (Bossink, Stalmeier, & De Weert, 1993; Brascamp, van Ee, Noest, Jacobs, & van den Berg, 2006; Mueller & Blake, 1989), violating one part of the proposition. Different limiting factors have been proposed to explain the infringement of the proposition: the role of periods of mixed perception (Mueller & Blake, 1989), the range of contrasts tested (Brascamp, van Ee, Noest, Jacobs, & van den Berg, 2006) and the role of return transitions (cases in which after a period of mixed perception dominance of the initial stimulus is re-establised, Bossink, Stalmeier, & De Weert, 1993).

In a recent study (Kang, 2009), evidence confirming and invalidating Levelt's second proposition has been reviewed and re-considered introducing new methods for testing binocular rivalry in order to elucidate the debate on its validity. Using new tracking methods, periods of mixed perception and return transition have been shown to be ineffective in explaining prolonged dominance of the stronger stimulus (in this study stimulus strength was manipulated by increasing contrast in one eye), while stimulus size has been proved to be crucial (Kang, 2009). When large visual stimuli were tested Levelt's second proposition was confirmed, while it was violated when small visual stimuli (subtending less than 1.5 degrees of visual angle) were tested. This finding was then corroborated by re-examining the literature and showing that small visual stimuli were used in previous studies that had disproved Levelt's second proposition (Table 1.3.1).

To clarify the importance of stimulus size in determining the validity of Levelt's second proposition Kang referred to a well-known local component of binocular rivalry (Alais, Lorenceau, Arrighi, & Cass, 2006; Blake, O'Shea, & Mueller, 1992) and proposed a model in which cooperation between local networks encoding small neighbouring areas of the visual field explained the three possible perceptual states during binocular rivalry (dominance of one or the other visual stimulus and periods of mixed perception). Activity of only one local detector violates the contrast-invariance envisaged by Levelt, but the combined output of the modelled local interacting networks replicates the predictions depicted by Levelt's second proposition. A slightly modified version of this model has recently been proposed by the same author (Kang & Blake, 2011) as a solution to integrate models of binocular rivalry spatio-temporal dynamics based on mutual inhibition between the eyes/stimuli, adaptation and noise. According to these authors rather than excluding each other, balance between these three phenomena would underlie the dynamics of binocular rivalry (Kang & Blake, 2011).

Study	**Stimulus**	**Size**	**Result**
(Levelt, 1965)	reversed	6.00°	**O**
(Fox & Rasche, 1969)	luminance	3.24°	**O**
(Bossink, Stalmeier, & De Weert, 1993)	contrast	1.32°	**X**
(Meng & Tong, 2004)	Sine wave grating	6°x2°	**O**
(Logothetis, Leopold, & Sheinberg, 1996)		3.00°	**O**
(Blake, 1977)		1.25°	**O**
(Mueller & Blake, 1989)		0.80°	**X**
(Brascamp, van Ee, Noest, Jacobs, & van den Berg, 2006)		0.62°	**X**

Table 1.3.1. Summary of studies on Levelt's second proposition. Adapted from (M. S. Kang, 2009). The result column indicates with O studies that validated the proposition and with X studies violating the proposition. Generally, studies confirming the proposition used large visual stimuli, whereas studies denying the proposition used small visual stimuli.

1.3.3 Onset Rivalry

As detailed in the previous paragraph, traditionally binocular rivalry dynamics have been described through the analysis of phase durations (average phase durations and distributions). As anticipated, the analysis of phase durations is important, for phase duration is a good index of binocular rivalry stability, with short phase durations indicating highly unstable visual perception with a very fast switching rate, and long phase durations indicating more stable visual perception with slow alternation rate and longer periods of constant perception of one or the other visual stimuli. Switching rate is also important because of its relation with stimulus strength, with rivalring visual stimuli eliciting a strong visual signal alternating more rapidly and weaker visual signals alternating slowly (Levelt, 1966, 1967). However, the analysis of phase durations is a collapsed measure of binocular rivalry dynamics that does not take into account the temporal order of events during a prolonged epochs of viewing.

Until recently, phase durations analysis was accepted as a standard measure, because following fusion of the dichoptic images binocular rivalry dynamics was thought to rely on common neural processes. Growing experimental evidence is though calling this assumption into question, demonstrating that the properties of initial rivalry are substantially different from those of sustained rivalry. Onset rivalry shows in fact a high degree of stability and predictability (for review see: Stanley, Forte, Cavanagh, & Carter, 2012), as opposed to the randomness shown by sustained binocular rivalry perceptual alternations (Fox & J., 1967; Kim, Grabowecky, & Suzuki, 2006; Lehky, 1995; Levelt, 1965; van Ee, 2009).

The most striking characteristic exhibited by onset rivalry is a stable bias in favour of one of the two dichoptic images that vary across the visual field (Carter & Cavanagh, 2007; Stanley, Carter, & Forte, 2011). At one particular location of the visual field, in fact the same visual stimulus is perceived at the onset of rivalry (fist coherent percept after binocular fusion) at every presentation. The perceptual bias is related to monocular dominance and stimulus contrast, but cannot be entirely explained by these two factors (Carter & Cavanagh, 2007; Stanley, Carter, & Forte, 2011). Furthermore, the onset bias is stable over time (weeks) for every observer and disappears when sustained rivalry is tested (Carter & Cavanagh, 2007).

As reported for sustained rivalry (Levelt, 1967), onset rivalry is influenced by stimulus strength, with the stronger visual stimulus being preferred over the weaker one (Chong & Blake, 2006) even for small imbalances between the eyes. On the other hand, while equating stimulus strength re-establishes perceptual balance between the eyes during sustained rivalry (both on total predominance and on mean phase durations), the stable bias characterizing onset rivalry resists also when luminance and contrast differences between the dichiptically presented visual stimuli is minimized for every observer (Stanley, Forte, Cavanagh, & Carter, 2012).

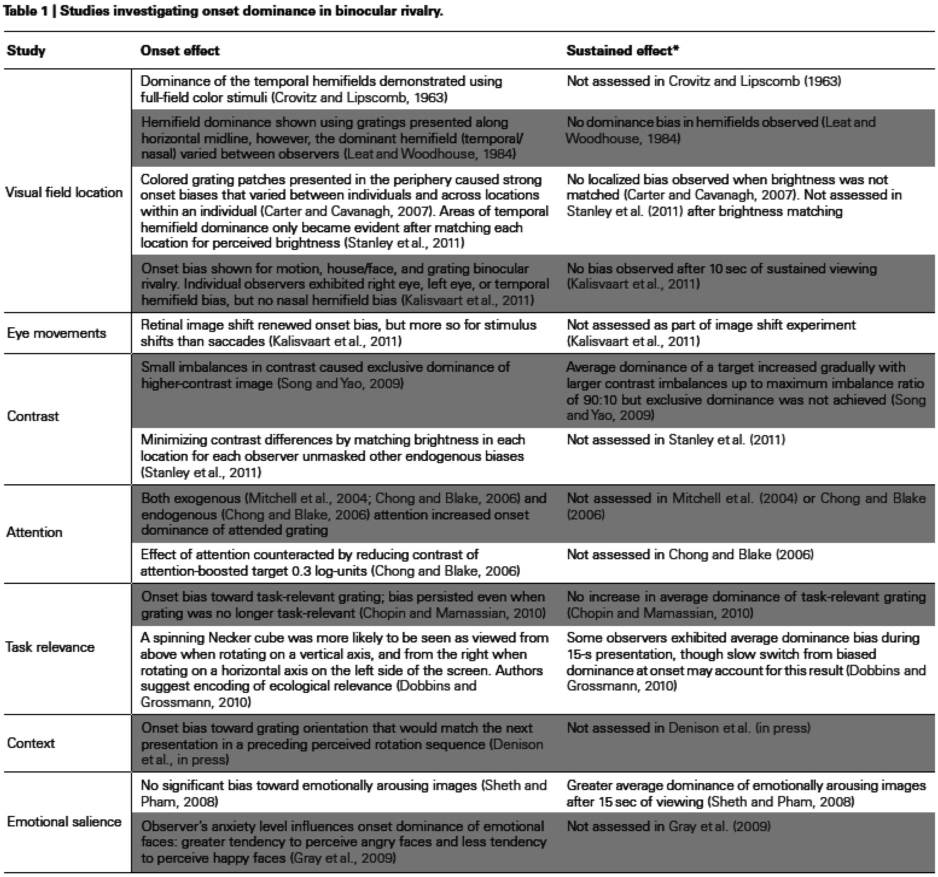


Table 1 | Studies investigating onset dominance in binocular rivalry.

Study	Onset effect	Sustained effect*
Visual field location	Dominance of the temporal hemifields demonstrated using full-field color stimuli (Crovitz and Lipscomb, 1963)	Not assessed in Crovitz and Lipscomb (1963)
	Hemifield dominance shown using gratings presented along horizontal midline, however, the dominant hemifield (temporal/nasal) varied between observers (Leat and Woodhouse, 1984)	No dominance bias in hemifields observed (Leat and Woodhouse, 1984)
	Colored grating patches presented in the periphery caused strong onset biases that varied between individuals and across locations within an individual (Carter and Cavanagh, 2007). Areas of temporal hemifield dominance only became evident after matching each location for perceived brightness (Stanley et al., 2011)	No localized bias observed when brightness was not matched (Carter and Cavanagh, 2007). Not assessed in Stanley et al. (2011) after brightness matching
	Onset bias shown for motion, house/face, and grating binocular rivalry. Individual observers exhibited right eye, left eye, or temporal hemifield bias, but no nasal hemifield bias (Kalisvaart et al., 2011)	No bias observed after 10 sec of sustained viewing (Kalisvaart et al., 2011)
Eye movements	Retinal image shift renewed onset bias, but more so for stimulus shifts than saccades (Kalisvaart et al., 2011)	Not assessed as part of image shift experiment (Kalisvaart et al., 2011)
Contrast	Small imbalances in contrast caused exclusive dominance of higher-contrast image (Song and Yao, 2009)	Average dominance of a target increased gradually with larger contrast imbalances up to maximum imbalance ratio of 90:10 but exclusive dominance was not achieved (Song and Yao, 2009)
	Minimizing contrast differences by matching brightness in each location for each observer unmasked other endogenous biases (Stanley et al., 2011)	Not assessed in Stanley et al. (2011)
Attention	Both exogenous (Mitchell et al., 2004; Chong and Blake, 2006) and endogenous (Chong and Blake, 2006) attention increased onset dominance of attended grating	Not assessed in Mitchell et al. (2004) or Chong and Blake (2006)
	Effect of attention counteracted by reducing contrast of attention-boosted target 0.3 log-units (Chong and Blake, 2006)	Not assessed in Chong and Blake (2006)
Task relevance	Onset bias toward task-relevant grating; bias persisted even when grating was no longer task-relevant (Chopin and Mamassian, 2010)	No increase in average dominance of task-relevant grating (Chopin and Mamassian, 2010)
	A spinning Necker cube was more likely to be seen as viewed from above when rotating on a vertical axis, and from the right when rotating on a horizontal axis on the left side of the screen. Authors suggest encoding of ecological relevance (Dobbins and Grossmann, 2010)	Some observers exhibited average dominance bias during 15-s presentation, though slow switch from biased dominance at onset may account for this result (Dobbins and Grossmann, 2010)
Context	Onset bias toward grating orientation that would match the next presentation in a preceding perceived rotation sequence (Denison et al., in press)	Not assessed in Denison et al. (in press)
Emotional salience	No significant bias toward emotionally arousing images (Sheth and Pham, 2008)	Greater average dominance of emotionally arousing images after 15 sec of viewing (Sheth and Pham, 2008)
	Observer's anxiety level influences onset dominance of emotional faces: greater tendency to perceive angry faces and less tendency to perceive happy faces (Gray et al., 2009)	Not assessed in Gray et al. (2009)

Table 1.3.2. Factors influencing onset and sustained rivalry differently. Adapted from (Stanley, Forte, Cavanagh, & Carter, 2012).

In synthesis, the initial bias in favour of one of the rivalring images seems to be guided both by exogenous and endogenous factors and cannot be explained by a single feature. Among the factors interacting in influencing onset rivalry are: zones of monocular dominance across the visual field (Carter & Cavanagh, 2007; Kalisvaart, Rampersad, & Goossens, 2011), imbalances in stimulus strength (Chong & Blake, 2006; Stanley, Carter, & Forte, 2011), both stimulus-driven (Chong & Blake, 2006; Hancock & Andrews, 2007; J. F. Mitchell, Stoner, & Reynolds, 2004) and voluntary (Chong & Blake, 2006) attention, the position of the visual target on the retina (Kalisvaart, Rampersad, & Goossens, 2011), learned utility of the visual stimulus (Chopin & Mamassian, 2010; Denison, Piazza, & Silver, 2011; Dobbins & Grossmann, 2010) and emotional saliency of the stimulus and observer anxiety level (Gray, Adams, & Garner, 2009; Sheth & Pham, 2008).

Table 1.3.2., adapted from (Stanley, Forte, Cavanagh, & Carter, 2012), reports all factors found to influence onset rivalry opposed to the very same factors influence on sustained rivalry. Interestingly, all of these factors have different effects on onset and sustained rivalry, suggesting that the two phenomena are guided by different neural mechanisms. To investigate the dynamics of binocular rivalry appropriately is therefore necessary to consider both processes, rather than limiting the analysis to phase durations.

1.4. Binocular Rivalry Suppression

One of the most fascinating aspects of binocular rivalry is the perceptual invisibility of a retinal image provoked by binocular rivalry suppression. While one of the stimuli dominates observer's perception the other image is removed from visual awareness until a perceptual switch occurs reversing dominance in favour of the previously suppressed stimulus. At which stage of neural processing does binocular rivalry suppression take place? What is the fate of the suppressed signal?

A method to quantify binocular rivalry suppression strength consists in measuring sensitivity to visual targets briefly presented on one of the rivalring images either during dominance or during suppression phases. The ratio between thresholds measured during suppression and those measured during dominance, once subtracted from 1, corresponds to an index of *suppression depth*, where 1 represents complete suppression (total invisibility of the visual target for all ranges of contrasts tested) and 0 represents no suppression (visual sensitivity during suppression equivalent to that during dominance). Surprisingly, despite its phenomenal invisibility, visual sensitivity during binocular rivalry suppression is only attenuated of around 0.3 to 0.5 log units, with suppression depth being generally comprised between 0.4 and 0.5 (Blake & Fox, 1974c; Nguyen, Freeman, & Alais, 2003; O'Shea & Crassini, 1981b; Ooi & Loop, 1994). Measuring suppression depth is particularly fascinating, for the method mimics "blindsight" conditions: under forced choice condition the observer reports a visual target correctly despite being consciously unaware of its presence.

The spared sensitivity found during suppression indicates that information related to the suppressed visual stimulus is not completely destroyed despite the total perceptual loss (Blake, 1989), demonstrating that a signal that is too weak to reach a conscious representation can nevertheless give rise to measurable behavioural effects and, consequently, neural activation. Interestingly, suppression depth has been shown to increase with stimulus complexity especially for visual stimuli eliciting responses along the ventral pathway (Alais & Melcher, 2007; Alais & Parker, 2006; Blake, 1989; Nguyen, Freeman, & Alais, 2003), suggesting a progressive disruption of the suppressed visual signal for different stages of visual analysis. To understand the nature and neural organization of binocular rivalry suppression different techniques have been used to investigate what can survive suppression, these include adaptation, priming, influence on the dominant stimulus and neurophysiologic recordings (fMRI in humans and electrophysiology in monkeys).

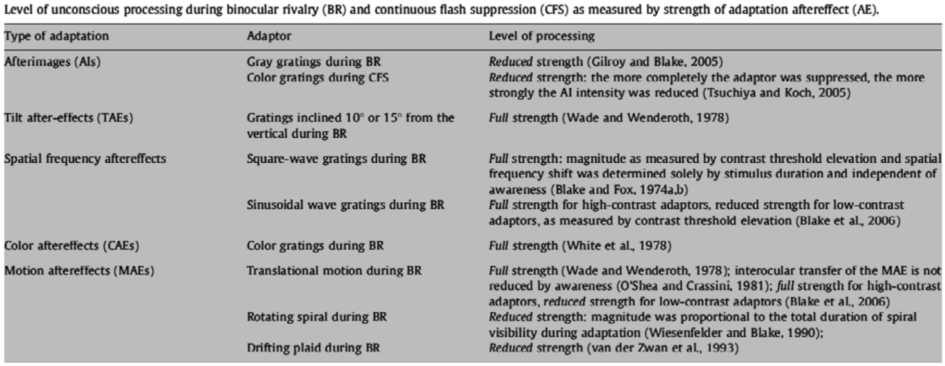
1.4.1 Visual adaptation and priming to suppressed patterns

The visual system is continuously adapting adjusting its sensitivity according to changes in the external world in order to allow efficient interaction with the environment (Clifford et al., 2007; Kohn, 2007). Adaptation is ubiquitous in the brain, occurring at different stages of visual processing, starting from the retina (e.g. light and dark adaptation, Shapley & Enroth-Cugell, 1984), to high level temporal visual cortices (e.g. face identity adaptation, Leopold, O'Toole, Vetter, & Blanz, 2001). Psychophysically, visual adaptation refers to the change in sensitivity (reduced responsiveness caused by neural fatigue) of a neural population after prolonged exposure to the preferred visual pattern (adaptor) that results in a subsequent alteration of the appearance of a related visual stimulus (test), called *adaptation aftereffect* (AE).

Visual adaptation has been considered as “the psychologist’s microelectrode” (Frisby, 1979), for it is a specific probe for the activity of different neural populations. Applied to the study of the neural correlates of visual awareness in general and binocular rivalry suppression, the idea is that if visual adaptation to a certain pattern can survive perceptual suppression of the adaptor stimulus, then suppression occurs at a farther stage of visual processing compared to that underlying the analysis of that particular pattern, a stage of neural processing that is therefore not directly involved in visual consciousness (Crick & Koch, 1995, , 1998; Koch, 2007).

The question is: to what extent can visual adaptation survive binocular rivalry suppression? Three are the possible outcomes when adapting to a visual stimulus rendered invisible by binocular rivalry suppression: *full-strength adaptation*, *reduced-strength adaptation*, *no adaptation*. Finding a reduced-strength adaptation when the adaptor is presented during suppression suggests that at that stage of neural processing binocular rivalry suppression is already operating attenuating, but not yet disrupting, neural responses to the suppressed image. When suppression is complete, no adaptation to the invisible stimulus would be observed, neural response to it being completely disrupted.

Suppression has been found to have no influence at all on the strength of some basic adaptation aftereffects, indicating that they can arise also in the absence of the adapting stimulus from visual awareness: the *tilt aftereffect* (adaptation to tilted lines resulting in briefly perceiving vertical lines as tilted in the opposite direction, Gibson & Radner, 1937), the *spatial frequency aftereffect* (adaptation to evenly spaced lines of a certain spatial frequency producing either a contrast threshold elevation, Blakemore & Campbell, 1969) or a perceptual shift in spatial frequency of the test stimulus presented immediately after adaptation, Blakemore & Sutton, 1969), *the orientation-contingent colour aftereffect* (extended viewing of pars of coloured gratings results in perceiving non-coloured gratings as tinted with the opposite colours, McCollough, 1965) and the *translational motion aftereffect* (prolonged exposure to contours linearly moving in one direction causing perception of static targets as moving in the opposite direction, Mather, Verstraten, & Anstis, 1998) are not affected by binocular rivalry suppression and show a strength that is comparable with that obtained when the adapting stimulus is presented monocularly or during dominance phases of binocular rivalry (Blake & Fox, 1974a, 1974b; Blake, Tadin, Sobel, Raissian, & Chong, 2006; O'Shea & Crassini, 1981a; Wade & Wenderoth, 1978). Consistently, motion priming (presenting a motion cue immediately before the presentation of bistable motion favours perception of the cued direction, Anstis & Ramachandran, 1987) has also be demonstrated to survive binocular rivalry suppression (Blake, Ahlstrom, & Alais, 1999), being effective even during periods of temporary invisibility. Table 1.4.1. summarizes the outcomes of studies on adaptation aftereffects during binocular rivalry suppression.



Level of unconscious processing during binocular rivalry (BR) and continuous flash suppression (CFS) as measured by strength of adaptation aftereffect (AE).

Type of adaptation	Adaptor	Level of processing
Afterimages (AIs)	Gray gratings during BR	*Reduced* strength (Gilroy and Blake, 2005)
	Color gratings during CFS	*Reduced* strength: the more completely the adaptor was suppressed, the more strongly the AI intensity was reduced (Tsuchiya and Koch, 2005)
Tilt after-effects (TAEs)	Gratings inclined 10° or 15° from the vertical during BR	*Full* strength (Wade and Wenderoth, 1978)
Spatial frequency aftereffects	Square-wave gratings during BR	*Full* strength: magnitude as measured by contrast threshold elevation and spatial frequency shift was determined solely by stimulus duration and independent of awareness (Blake and Fox, 1974a,b)
	Sinusoidal wave gratings during BR	*Full* strength for high-contrast adaptors, reduced strength for low-contrast adaptors, as measured by contrast threshold elevation (Blake et al., 2006)
Color aftereffects (CAEs)	Color gratings during BR	*Full* strength (White et al., 1978)
Motion aftereffects (MAEs)	Translational motion during BR	*Full* strength (Wade and Wenderoth, 1978); interocular transfer of the MAE is not reduced by awareness (O'Shea and Crassini, 1981); *full* strength for high-contrast adaptors, *reduced* strength for low-contrast adaptors (Blake et al., 2006)
	Rotating spiral during BR	*Reduced* strength: magnitude was proportional to the total duration of spiral visibility during adaptation (Wiesenfelder and Blake, 1990);
	Drifting plaid during BR	*Reduced* strength (van der Zwan et al., 1993)

Table 1.4.1. Adaptation Aftereffects (AE) measured during binocular rivalry suppression. Adapted from (Crick & Koch, 1998; Lin & He, 2009).

Other types of adaptation aftereffects are only partially disrupted by binocular rivalry suppression and show a reduced strength compared to monocular conditions: *negative afterimages* (the illusory image appearing after exposure to a bright image, Craik, 1940) and complex forms of the motion after effect as *spiral motion, drifting plaid* and *optic flow* aftereffects (Mather, Verstraten, & Anstis, 1998) show reduced effect when the adaptor is suppressed during rivalry (Blake, 1997; Gilroy & Blake, 2005; Tsuchiya & Koch, 2005; van der Zwan, Wenderoth, & Alais, 1993).

One difficulty arising when testing adaptation during suppression is that because of the stochastic nature of perceptual alternation during binocular rivalry, the duration of the current suppressed phase is unpredictable, leading to non-homogeneous adaptation durations and to possible overlap of adaptation with dominance. These two methodological confounds could possibly underpin the survival of adaptation aftereffects found during perceptual suppression. In line with this idea, Blake et al (2006) have demonstrated that the strength of the preserved aftereffects depends on the proportion of time during which the adaptor had been effectively removed from awareness (Blake, Tadin, Sobel, Raissian, & Chong, 2006). They found reduced adaptation threshold elevation and motion aftereffects when effective suppression duration was controlled. These authors also demonstrated that the strength of the spared adaptation aftereffect depended on contrast of the adapting stimulus, with lower contrast adaptors effect being more sensitive to binocular rivalry suppression.

To compensate for the uneven, random duration of binocular rivalry suppression phases, in recent studies the method of *continuous flash suppression* (CFS) has also been used, for it allows deep and constant suppression of a salient visual stimulus over extended periods of time (Tsuchiya & Koch, 2005). When one eye is continuously flashed with different, contour-rich, high-contrast random patterns (white noise, Mondrian patterns, scrambled images) at about 10 Hz (i.e. 100 ms per pattern), information presented to the other eye is perceptually suppressed for extended periods of time (up to 3 minutes or more, Figure 1.4.1.). Suppression provoked by the continuous flashes has been shown to summate, resulting not only in longer suppression periods, but also in deeper suppression of the other eye: detection thresholds of probes presented to the suppressed eye during CFS are in fact elevated of a 20-fold factor compared to monocular viewing, compared with a 3-fold elevation observed during binocular rivalry (Tsuchiya, Koch, Gilroy, & Blake, 2006).

Interestingly, the adaptation aftereffects surviving binocular rivalry suppression or being attenuated and not abolished by suppression originate from neural alteration in early visual cortices (V1-V2) entirely (Blakemore, Carpenter, & Georgeson, 1970; Carpenter & Blakemore, 1973; Humphrey & Goodale, 1998; Maffei & Fiorentini, 1973; Morrone, Burr, & Maffei, 1982; Shimojo, Kamitani, & Nishida, 2001) or in part (Huk, Ress, & Heeger, 2001; Movshon & Lennie, 1979), suggesting that binocular rivalry suppression starts to be effective at the level of primary visual cortex, but it is not complete at that stage of visual processing.

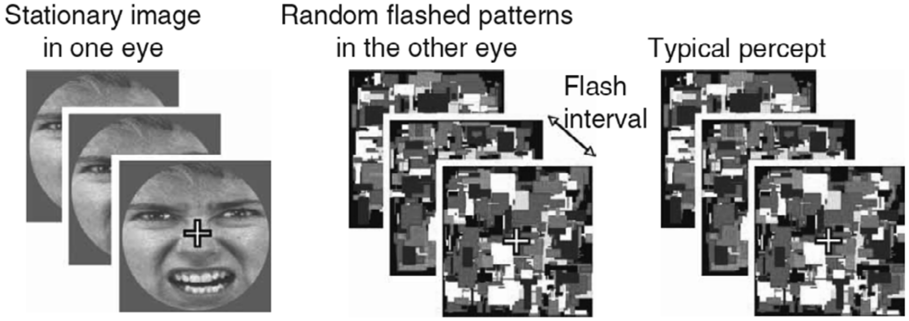


Figure 1.4.1. Continuous Flash suppression. Adapted from (Tsuchiya & Koch, 2005) Continuously flashed Mondrian patterns (10 Hz) in one eye provoke deep and stable perceptual suppression of salient images presented to the other eye for a prolonged period of time (up to 3 minutes or more).

In general, simple, basic visual stimuli that elicit responses early in the visual system are only partially affected by binocular rivalry suppression that instead completely conceals responses to complex visual stimuli elaborated by higher order visual areas. In line with this idea, the rotating optic flow motion aftereffect (Wiesenfelder & Blake, 1990) as well as the paid induced motion aftereffect (van der Zwan, Wenderoth, & Alais, 1993), the face identity aftereffect (Moradi, Koch, & Shimojo, 2005) and the illusory contour aftereffect (van der Zwan & Wenderoth, 1994) are totally abolished when the adaptor is presented during periods of invisibility during binocular rivalry, these visual stimuli need therefore a conscious processing in order to be effective (Lin & He, 2009).

The same trend is shown by visual priming experiments engaging complex stimuli: picture naming priming (advantage in reaction times and accuracy when naming visual pictures that had been previously presented even accidentally (Tulving & Schacter, 1990)) and word priming (fast recognition of scrambled words with prior exposure to words belonging to the same category, Meyer & Schvaneveldt, 1971) are both abolished if the priming stimulus is presented during binocular rivalry suppression (Cave, Blake, & McNamara, 1998; Zimba & Blake, 1983). Coherently with this line of evidence, ERP responses (N400) to meaningful visual stimuli have been found to be silenced by binocular rivalry suppression (Kang, Blake, & Woodman, 2011). The complex visual stimuli listed above are elaborated by visual areas at a subsequent stage compared to the early cortices in which neural activity is only reduced by suppression. This evidence supports a hierarchical organization of binocular rivalry, with suppression depth increasing with increasing complexity of the visual stimuli and along both the dorsal and the ventral visual pathway (Nguyen, Freeman, & Alais, 2003).

1.4.2. Where does suppression take place in the visual brain?

The attenuation of neural responses caused by binocular rivalry suppression has been demonstrated to initiate early in the visual system, with BOLD signal amplitude awareness-dependent fluctuations being measured already at the thalamic level in LGN (Haynes, Deichmann, & Rees, 2005; Wunderlich, Schneider, & Kastner, 2005) and in monocular regions of the primary visual cortex, as demonstrated by Tong and Engel using a clever experimental paradigm taking advantage of the blind-spot representation (Tong & Engel, 2001). Neural activity modulation reflecting perceptual states of binocular rivalry has been further demonstrated at the level of the primary visual cortex using neuroimaging techniques (Levi, 2005; Lumer, Friston, & Rees, 1998; Polonsky, Blake, Braun, & Heeger, 2000), indicating that binocular rivalry suppression is already effective in V1, that is therefore involved in awareness. Furthermore, BOLD signal modulation in V1 has also been demonstrated to reflect the perceptual travelling waves experienced by the observer during transition periods following retinotopic maps (Lee, Blake, & Heeger, 2007). The role of the primary visual cortex in mediating visual awareness has been also confirmed by Haynes and Rees, showing that V1 activity during binocular rivalry when analyzed by a support-vector machine could predict the observer's conscious state with accuracy approaching 100% (Haynes & Rees, 2005).

The BOLD signal is a measure of the concentration of metabolic markers reflecting only indirectly neural activity modulation that also comprises neural events other than action potentials (Logothetis, 2003), using other neuroimaging techniques that measure neural activity directly is useful for expanding and reinforcing the evidence of an involvement of early visual cortices in mediating perceptual alternations during binocular rivalry. Fluctuations of the signal strength coupled with binocular rivalry alternations have been revealed using EEG techniques (VER, visual evoked responses, Brown & Norcia, 1997; de Labra & Valle-Inclan, 2001; Roeber & Schroger, 2004) and MEG (magnetoencephalography, Srinivasan & Petrovic, 2006; Tononi, Srinivasan, Russell, & Edelman, 1998), that provide a direct measure of cerebral activity but cannot precisely localize the neural locus where that activity is originated because of the low spatial resolution provided by the two techniques.

Taken together, the psychophysical results showing attenuation, but not cancellation of adaptation aftereffects thought to reflect neuronal activity in primary visual cortex and the neuroimaging evidence listed above, demonstrate that binocular rivalry suppression inhibits V1 activity to a certain extent, but does not extinguish early visual responses, for basic visual information can be analyzed despite perceptual suppression. This is confirmed by evidence showing that when suppressed by binocular rivalry, early visual features such as orientation (Pearson & Clifford, 2005a; Stuit, Paffen, van der Smagt, & Verstraten, 2011) and colour (Hong & Shevell, 2009) of a visual stimulus can alter the appearance of the dominant stimulus, escaping suppression mechanisms.

At the first stages of visual analysis suppression is not complete, some information survives even if weakened compared to dominance. Ascending the hierarchy of visual processing, suppression is thought to increase in depth both along the ventral and the dorsal pathway (Goodale & Milner, 1992), as demonstrated by psychophysical evidence measuring detection thresholds to probes presented during suppression of visual stimuli of increasing complexity, that are therefore processed by visual areas at different levels (Alais & Melcher, 2007; Nguyen, Freeman, & Alais, 2003).

Further evidence in favour of an increasing strength of suppression proceeding along the stream of visual analysis comes from electrophysiological recordings in awake monkeys experiencing binocular rivalry (Leopold & Logothetis, 1996; Sheinberg & Logothetis, 1997): the number of neurons showing reduced responses during suppression phases of binocular rivalry augments progressing along the visual pathway (Figure 1.4.2.), with total response suppression being achieved in inferotemporal cortex (IT), that comprises an ensemble of object selective areas encoding complex objects in a view- and position-invariant way (Ungerleider, Galkin, & Mishkin, 1983).

The disruption of neural activity caused by binocular rivalry suppression in these high-level visual areas is responsible for the failure of suppressed complex images in surviving binocular rivalry suppression, for the annihilation of IT responses results in impaired object recognition and semantic processing, explaining the absence of picture naming and word priming (Cave, Blake, & McNamara, 1998; Zimba & Blake, 1983), as well as the lack of adaptation to complex objects like faces (Moradi, Koch, & Shimojo, 2005) observed during suppression. Similar results have been obtained measuring BOLD responses in high-level visual areas both of the dorsal (Moutoussis, Keliris, Kourtzi, & Logothetis, 2005) and of the ventral pathway (Moutoussis & Zeki, 2002; Tong, Nakayama, Vaughan, & Kanwisher, 1998). For example, Tong et al (1998) measured BOLD responses in the human fusiform face area (FFA) and the parahippocampal place area (PPA) during binocular rivalry between faces and house stimuli presented dichoptically (Tong, Nakayama, Vaughan, & Kanwisher, 1998). The FFA is a face-selective area that is activated by faces and not by other visual objects (Kanwisher, McDermott, & Chun, 1997), while the PPA is selectively activated by places but does not respond to faces (Epstein & Kanwisher, 1998). Interestingly, Tong et al found that BOLD activity in those selective areas followed observer's visual perception, fluctuating according to reported perceptual alternations. Moreover, the amplitude of the BOLD response measured during binocular rivalry was comparable to that measured during non-rivalrous perception (Figure 1.4.3.). This results demonstrate that in object-selective areas of the human brain binocular rivalry is completely resolved, with neural activity reflecting only conscious perception (Tong, Nakayama, Vaughan, & Kanwisher, 1998).

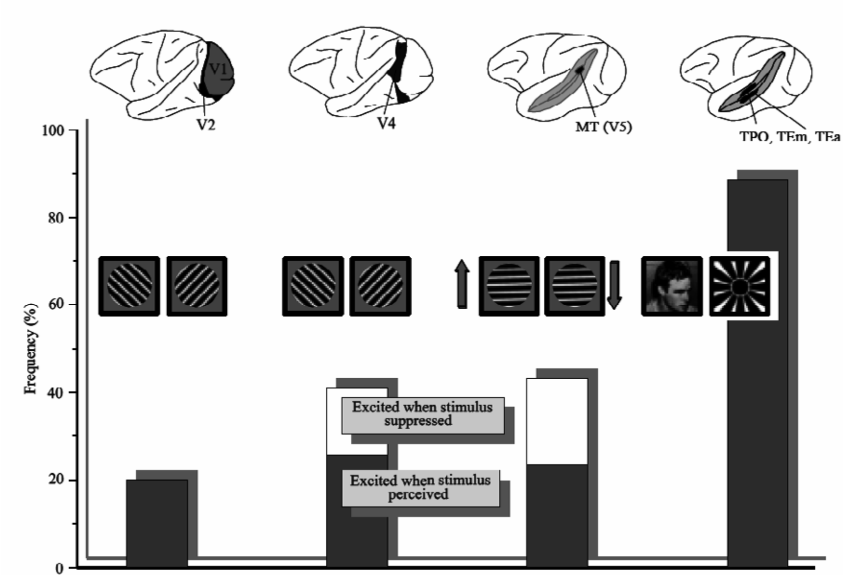


Figure 1.4.2. Distribution of perception-related activity in the monkey’s visual cortex. Adapted from (Logothetis, 1998). The number of neurons showing perception-modulated activity increases along the visual pathway and is maximum (91% of total neurons) in the IT cortex when monkeys are presented with binocular rivalry between complex visual stimuli.

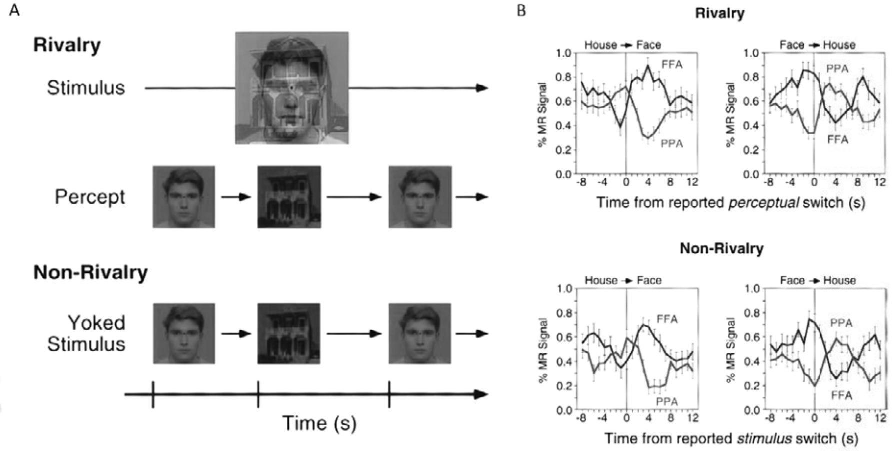


Figure 1.4.3. Bold activity in FFA and PPA measured during binocular rivalry and during non-rivalrous stimulation. Adapted from (Tong, Nakayama, Vaughan, & Kanwisher, 1998). While lying in a magnetic resonance imaging (MRI) scanner, the observer is presented with dichoptic complex visual stimuli (house and face, panel A) generating binocular rivalry. The amplitude of the BOLD signal in PPA and FFA (high level extrastriate areas in the temporal cortex) was modulated following observer’s perception during rivalry and was almost identical to that observed during rivalry replay (Panel B).

An exceptional insight into the neural mechanisms underlying binocular rivalry dynamics in the human ventral visual pathway has been obtained by Kreiman, Fried and Koch (2002), who measured in vivo single neurons responses in the medial temporal lobe (MLT) of human observers implanted with depth electrodes to localize the focus of seizure onset in pharmacologically untreatable epilepsy (Kreiman, Fried, & Koch, 2002). When binocular rivalry (in the form of flash suppression, Blake, Westendorf, & Fox, 1990; Wolfe, 1984) between the stimulus preferred by the cell and a random pattern was presented, the neuron responded during dominance of the preferred image (e.g. Bill Clinton's face) and was silenced during its suppression (Figure 1.4.4.), showing that MTL neurons activity followed visual perception during rivalry, reflecting the observer's conscious perception.

A large amount of evidence has been cumulating showing that binocular rivalry suppression totally abolishes neural activity along the ventral (*vision-for-perception*) visual pathway, but the same does not hold for the dorsal (*vision-for-action*) pathway (Goodale & Milner, 1992). Psychophysically, the fate of suppressed visual signals processed by the dorsal pathway has been demonstrated to be less dramatic than that of visual stimuli processed along the ventral pathway (e.g. faces, complex objects, meaningful scenes). For example, the suppressed direction of motion has been found to alter the dominant direction of motion (complex motion is processed by the dorsal area V5-MT and the MT+ complex, Born & Bradley, 2005) when small visual stimuli are tested (Andrews & Blakemore, 1999) and priming to manipulable objects (processed by the dorsal areas V3A and V7 and IPS, Grill-Spector, Kushnir, Edelman, Itzchak, & Malach, 1998; Grill-Spector, Kushnir, Hendler, & Malach, 2000) has been shown to survive binocular rivalry suppression in a categorization task (Almeida, Mahon, Nakayama, & Caramazza, 2008). Similarly a residual BOLD activation has been found in response to images of manipulable tools rendered perceptually invisible by CFS (Fang & He, 2005). Finally, suppression of rivalring visual stimuli can be shortened when the observer voluntary controls the direction of motion of the suppressed visual stimulus (Maruya, Yang, & Blake, 2007). That some trace of perceptually suppressed image can be retained by the dorsal pathway agrees with the model proposed by Goodale and Milner (1992), according to which the dorsal pathway encodes visual information useful for action and not for object recognition, and is therefore not necessarily linked to visual awareness (Goodale & Milner, 1992).

Faces are a special category of visual stimuli, with a dedicated visual area (FFA, Kanwisher, McDermott, & Chun, 1997). Even though binocular rivalry suppression destroys neural activity in the FFA (Tong, Nakayama, Vaughan, & Kanwisher, 1998), some information conveyed by facial expression can survive suppression. Visual information charged with a negative emotion is thought to be processed by the visual system in an compulsory, non-conscious way, automatically capturing attention taking advantage of priority processing, for rapidly detecting threats is essential for survival. For example, angry, threatening faces have been shown to have a perceptual advantage over happy or neutral faces in visual search, known as “anger superiority” (Hansen & Hansen, 1988). In line with this evidence, BOLD activity has been found in the left amygdala and in the STS in response to fearful faces rendered invisible by binocular rivalry suppression (Jiang & He, 2006; Pasley, Mayes, & Schultz, 2004; Williams, Morris, McGlone, Abbott, & Mattingley, 2004), while no response to neutral faces was recorded. Psychophysically, images of fearful faces have been found to be suppressed for a shorter time compared to happy and neutral faces during CFS (Stein & Sterzer, 2012; Sterzer, Hilgenfeldt, Freudenberg, Bermpohl, & Adli, 2011; Tsuchiya, Moradi, Felsen, Yamazaki, & Adolphs, 2009; Williams, Morris, McGlone, Abbott, & Mattingley, 2004; Yang, Zald, & Blake, 2007). Consistently with the idea of a privileged conscious access for emotional information, an initial bias in favour of threatening faces has been demonstrated to be stronger in individual with an anxiety disorder (Singer, Eapen, Grillon, Ungerleider, & Hendler, 2012). Finally, emotional arousing images (e.g. nudity) have been shown to escape perceptual suppression caused by CFS (Jiang, Costello, Fang, Huang, & He, 2006).

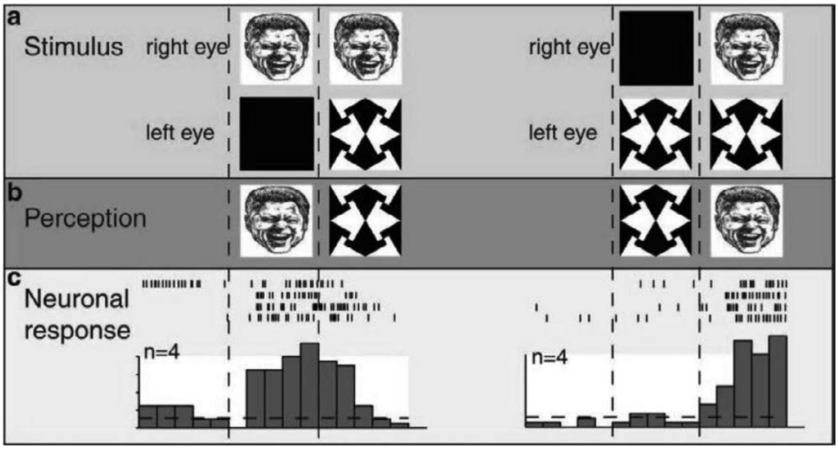


Figure 1.4.4. Single cell response to the preferred stimulus during binocular rivalry in human medial temporal lobe (MLT). Adapted from (Kreiman, Fried, & Koch, 2002).

In general, investigating the fate of suppressed visual images is a unique tool to understand the neural mechanisms underlying conscious visual perception (Crick & Koch, 1998; Lin & He, 2009). To summarize, binocular rivalry suppression is already effective at early stages of visual analysis (LGN, primary visual cortex), where the signal associated with the suppressed image is reduced in strength, but not destroyed. Information processed by these early visual areas, though weakened, survives suppression and can be used outside of visual awareness, as demonstrated by adaptation and priming experiments as well as by experiment showing that the suppressed image can alter the appearance of the dominant one. Ascending the visual hierarchy, suppression increases in depth, especially along the ventral pathway, where suppressed visual information about complex objects and meaningful images is disrupted. Complex stimuli can escape binocular rivalry suppression when they provide a behavioural advantage, either for action (e.g. manipulable tools) or for reaction to threat (e.g. fearful faces), gaining a priority access to consciousness.

1.5. Binocular Rivalry and Attention.

Binocular rivalry and selective attention share similar characteristics and an overlapping neural network, that is why the two phenomena have been proposed to be strictly linked. Both selective attention and rivalry, in fact, involve a perceptual choice among competing visual stimuli, with a winner-takes-it-all outcome in which the selected image dominates over the non-selected one (Leopold & Logothetis, 1999). Furthermore, a distributed fronto-parieto-occipital network of cerebral areas has been shown to be crucial both for the exertion of top-down attentional selection (Corbetta & Shulman, 2002; Desimone & Duncan, 1995; Kastner & Ungerleider, 2000; Posner & Dehaene, 1994) and for binocular rivalry (Cosmelli et al., 2004; Knapen, Brascamp, Pearson, van Ee, & Blake, 2011; Lumer, Friston, & Rees, 1998; Miller et al., 2000; Srinivasan, Russell, Edelman, & Tononi, 1999; Sterzer & Rees, 2008). Figure 1.5.1. shows the neural network mediating selective attention (panel A) and rivalry (panel B), note that in the case of binocular rivalry it is not clear whether the stronger activity found in the fronto-parietal network for binocular rivalry vs pseudo-rivalry display reflects a feedback or a feedforward signal with early visual areas involved in processing binocular rivalry.

The role of attention on the dynamics of binocular rivalry has been attracting the interest of visual scientists since the discovery of binocular rivalry itself. When describing tor the first time binocular rivalry in 1838, Wheatstone made the observation that “it does not appear to be in the power of the will to determine the appearance of either of the two letters” (see paragraph 1.1.1. for the extended quote of Wheatstone, 1838), raising therefore the question whether binocular rivalry could be under the control of voluntary attention. Unlike Wheatstone, almost one century later, Herman von Helmoltz (1925) considered binocular rivalry as a “psychic act”, for he claimed that he could voluntarily control the dynamics of binocular rivalry selecting one or the other image according to his will. Fom this result Helmoltz concluded that binocular rivalry was a high-level phenomenon (Helmoltz, 1925). However, the early studies on attentional control over binocular rivalry did not control for eye movements, that have been shown to interact with binocular rivalry both by influencing dominance of one image over the other and by influencing switching rate (Kalisvaart, Rampersad, & Goossens, 2011; Peckham, 1936; van Dam & van Ee, 2006).

The first systematic study on the role of attention on the dynamics of binocular rivalry dates back to 1978, when Lack reviewed the literature and performed carefully designed experiments in which he demonstrated that perceptual alternations during binocular rivalry could be modulated by selective attention even after that peripheral factors like eye-movements were ruled out, and that the amount of attentional influence on binocular rivalry increased with practice (Lack, 1978). Interestingly, the same conclusion was drawn almost 30 years later by Van Dam and Van Ee (2006), that re-considered the role of saccadic eye-movements in mediating attentional control over rivalry. These authors found a correlation between the exertion of saccades and the occurrence of perceptual switches, so that observers could use eye-movements to trigger an alternation, but they failed in finding a difference in eye movements rate between normal viewing conditions and conditions in which observers were asked to attentionally modulate rivalrous perception, van Dam & van Ee, 2006). Even though Lack clearly showed that attention could play a role in biasing binocular rivalry, Helmoltz’ belief that binocular rivalry depended on attentional selection and was under complete attentional control (Helmoltz, 1925) has been reexamined, the role of attention being scaled down to modulation rather than control over rivalry.

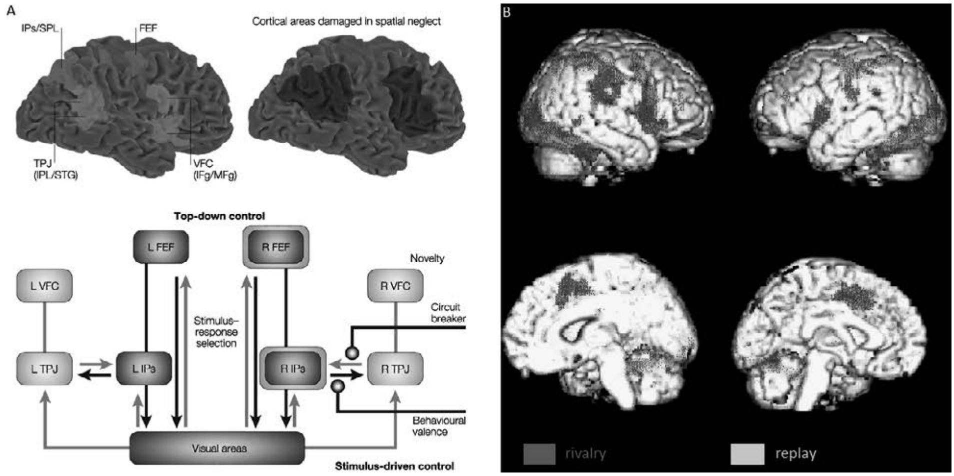


Figure 1.5.1. Fronto-parietal neural networks involved in selective attention (A) and binocular rivalry (B). (A) adapted from (Corbetta & Shulman, 2002) and (B) adapted from (Lumer, Friston, & Rees, 1998))

In the next paragraphs we will review recent studies investigating the role of attention on binocular rivalry separately for voluntary/endogenous attention and involuntary/exogenous attention. Voluntary attention refers to an active selection of a visual stimulus by the observer, reflecting a top-down process, while exogenous attention refers to an automatic selection in which a particular feature of a visual stimulus captures observer's attention and reflects therefore a bottom-up process (Bundesen & Habekost, 2008; Wright & Frenzel, 2008).

1.5.1. Voluntary/Endogenous attention and binocular rivalry

After Lack's observations (Lack, 1978), research on the modulatory effects of binocular rivalry has been taken up by Ooi and He (1999), who exploited the Cheshire Cat effect (Duensing & Miller, 1979) that occurs when one eye is presented with an image, while a blank is presented to the other eye. Under these conditions, the image dominates over the blank, introducing a perturbation in the visual field of the eye that sees the blank leads the image presented to the other eye to be suppressed. Ooi and He (1999) found that driving voluntary attention to a rivalring stimulus counteracted the tendency of the Cheshire Cat effect to suppress the image, voluntary attention retaining the selected visual stimulus dominant for longer periods (Ooi & He, 1999).

A similar result was found in a study performed by Meng & Tong, who confronted the role of attention in mediating bistable perception and binocular rivalry (Meng & Tong, 2004). When the authors instructed participants to voluntarily hold one of the rivalring images at the expenses of the other, they found that attentive modulation of rivalry was possible (Figure 1.5.2.), but that observers could only slightly lengthen dominance of the attended visual stimulus (+13% on average), whereas, attentional control over another bistable visual stimulus (Necker cube) was stronger (+37% on average). One year later, van Ee, van Dam and Brouwer confirmed the resistance of binocular rivalry to voluntary attention compared to other types of bistable stimuli (van Ee, van Dam, & Brouwer, 2005).

From this result, Meng & Tong concluded that binocular rivalry was a more automatic, stimulus-driven process compared to bistable perception, being probably mediated by lower-level neural events (Meng & Tong, 2004). Coherently with this hypothesis, in another experiment Meng & Tong found that observers' voluntary modulation of overall switching rate was as strong for binocular rivalry than for the Necker cube, showing that alternation rate modulation and selection of one image are distinct processes, the first being mediated by lower-level mechanisms (switching rate is in fact influenced by low level, physiological factors like, for example eye blinks, Peckham, 1936, and can be changed by modulating stimulus strength, see paragraph 1.2.3 , with stronger stimuli alternating faster, Levelt, 1966).

The distinction between selection of a particular visual stimulus and modulation of switching rate has been confirmed by Paffen, Alais and Verstraten (2006), who demonstrated that alternation rate during binocular rivalry was slower when attention was diverted from the rivalring stimuli (orthogonal gratings) by a concurrent visual task (surround motion direction discrimination). The slowdown of the switching rate also correlated with the difficulty of the concurrent task and was similar to the effect of reducing contrast of the rivalring images (Levelt, 1966), from this the authors concluded that attention acts on binocular rivalry by actually boosting the apparent contrast of the visual stimuli, speeding therefore the alternation rate (Paffen, Alais, & Verstraten, 2006).

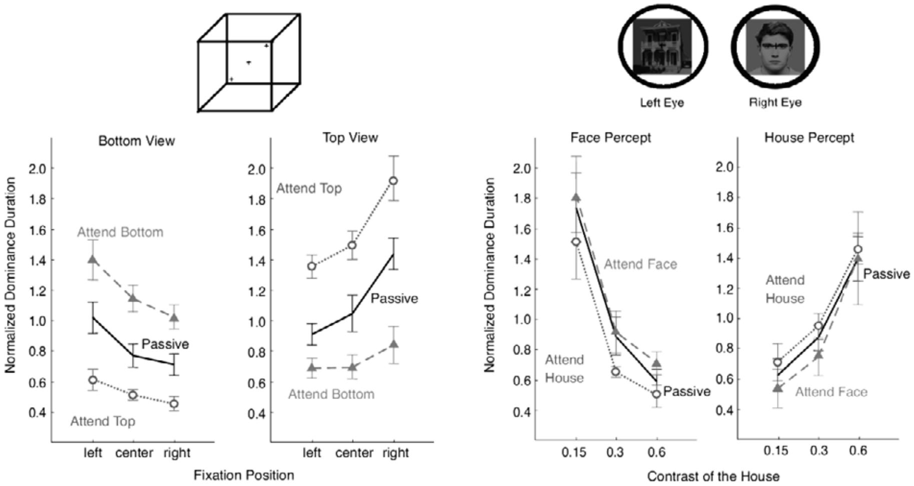


Figure 1.5.2. Influence of voluntary attention on the dynamics of bistable perception (Necker cube) and binocular rivalry. Adapted from (Meng & Tong, 2004)
When asked to attend to one of the two bistable visual stimuli by holding it in dominance, observer's attentional control was greater on the Necker cube (Panel A) than on binocular rivalry (Panel B).

Several other studies have proposed that attention interacts with binocular rivalry by increasing effective contrast of the visual stimuli (Chong & Blake, 2006; Chong, Tadin, & Blake, 2005; Paffen, Alais, & Verstraten, 2006; Paffen, Hooge, Benjamins, & Hogendoorn, 2011), for attending to a visual stimulus has been shown to increase its apparent contrast (Carrasco, Ling, & Read, 2004) and also to affect neural responses in a similar way to that of contrast increasing (Reynolds & Chelazzi, 2004). This interpretation is still debated, because the effect of attention seems to violate Levelt's second proposition that increasing contrast in one eye shortens durations of the stimulus presented to the other eye and therefore diminish suppression of the stronger visual stimulus (Levelt, 1965). For example, Chong, Tadin and Blake (2005) have shown that performing an attentional task on one of the rivalring stimuli (i.e. monitoring small changes in spatial frequency) increases dominance duration of the attended stimulus up to +50% compared to baseline, but does not affect the other stimulus duration (Chong, Tadin, & Blake, 2005).

This experiment shows that attentional modulation of binocular rivalry can be enhanced increasing behavioural relevance of the visual stimuli and task (+50% modulation compared to +13% found by Meng and Tong, 2004), but argues against the "increasing apparent contrast" interpretation of the effect of attention on binocular rivalry, for it clearly violates Levelt's second proposition (Levelt, 1965). An accepted explanation of this violation is that one cannot voluntarily attend to an unseen visual stimulus and therefore voluntarily attention cannot interact with a suppression phase during rivalry. In this light, the result obtained by Hancock and Andrews (2007) is controversial, for it is the only evidence showing an effect of voluntary attention both on dominance and on suppression of the attended stimulus (Hancock & Andrews, 2007).

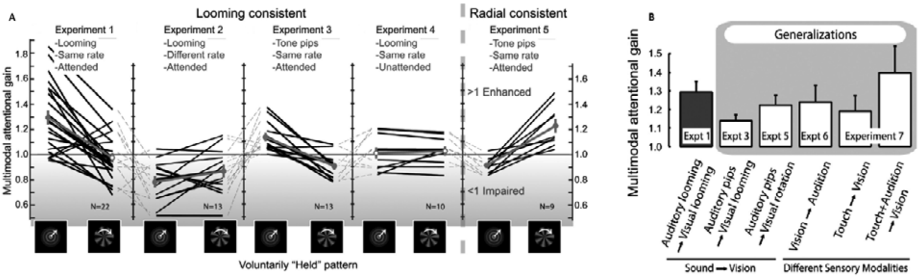


Figure 1.5.3. Attentional gain on binocular rivalry provoked by a congruent sound. Adapted from (van Ee, van Boxtel, Parker, & Alais, 2009)
Attentional modulation on binocular rivalry between a looming visual stimulus and a rotating radiant grating is enhanced by the concomitant presentation of a congruent auditory (Panel A) or tactile stimulus. The auditory signal does not bias binocular rivalry dynamics on its own (Experiment 4), but is effective in boosting attentional modulation on the rivalring congruent percept. Increasing behavioural relevance increases attentional gain, that is maximum for trimodal stimulation (audition + touch, Panel B).

The importance of behavioural relevance in enhancing effectiveness of attention in influencing the dynamics of binocular rivalry has been confirmed by a recent study (van Ee, van Boxtel, Parker, & Alais, 2009) showing that attentional control over one of the rivalring visual stimuli can be enhanced if a congruent signal is presented in another sensory modality (audition). The authors also demonstrated that, in order to observe the attentional gain, the auditory signal needed to be perfectly synchronized with the looming frequency of the attended visual signal (Figure 1.5.3.A) and that increasing behavioural relevance by introducing another congruent signal (touch) further increased the attentional gain (Figure 1.5.3.B). Interestingly, the congruent auditory stimulus enhanced attentional modulation of binocular rivalry only by prolonging dominance of the attended visual stimulus and did not affect its suppression, a result that agrees with the majority of the literature (Chong, Tadin, & Blake, 2005; Meng & Tong, 2004; Paffen & Alais, 2012; van Ee, Noest, Brascamp, & van den Berg, 2006; van Ee, van Dam, & Brouwer, 2005).

1.5.2. Involuntary/Exogenous attention and binocular rivalry

Exogenous attention reflects a bottom-up modulation of neural activity triggered by a salient visual stimulus that automatically attracts attention (Bundesen & Habekost, 2008; Wright & Frenzel, 2008). Endogenous and exogenous attention are two distinct processes that are thought to be elaborated by different neural networks (Corbetta, Kincade, & Shulman, 2002; Posner & Dehaene, 1994), it is therefore plausible that they have different effects on the dynamics of binocular rivalry, that is a complex phenomenon mediated by a distributed neural network (Alais & Blake, 2005; Blake & Logothetis, 2002; Tong, Meng, & Blake, 2006).

As discussed in the previous paragraph, voluntary attention influences binocular rivalry mainly by prolonging dominance duration of the attended image. In 1999 Ooi and He investigated whether, differently from voluntary attention, involuntary attention could revert a suppressed image to dominance. It is well known that a transient change presented to the suppressed image can produce a perceptual switch (Walker & Powell, 1979), taking advantage of this phenomenon, Ooi and He introduced a pop-out element in the suppressed image, that attracted automatically exogenous attention and found that involuntary attention attracted to a cued location had the effect of bringing back the suppressed image to dominance (Ooi & He, 1999). Similarly, Paffen and Von der Stigchel (2010) found that a pop out cue to a particular location of the visual field increased the occurrence of perceptual switches to the rivalring stimuli presented in the cued locations and concluded that exogenous attention is able to initiate a perceptual alternation rescuing the suppressed visual signal (Paffen & Van der Stigchel, 2010).

Object-based exogenous attention has also been found to strongly bias the onset of rivalry, that, as discussed in paragraph 1.3.3. is thought to be a distinct, though related process compared to sustained rivalry (Stanley, Forte, Cavanagh, & Carter, 2012). For example, if prior to the onset of rivalry attention is exogenously cued by briefly translational movement of one of two overimposed transparent rotating textures (Figure 1.5.4.), onset rivalry will be biased in favor of the cued surface (Mitchell, Stoner, & Reynolds, 2004). A similar result has then been obtained by Chong and Blake (2006) using as visual stimuli orthogonal gratings and as exogenous cue an increment in contrast or a little orientation change (Chong & Blake, 2006), and by Hancock and Andrews (Hancock & Andrews, 2007). Chong and Blake also reported that onset rivalry could be biased by voluntarily orienting attention to one of the rivalring stimuli before the dichoptic presentation (Chong & Blake, 2006).

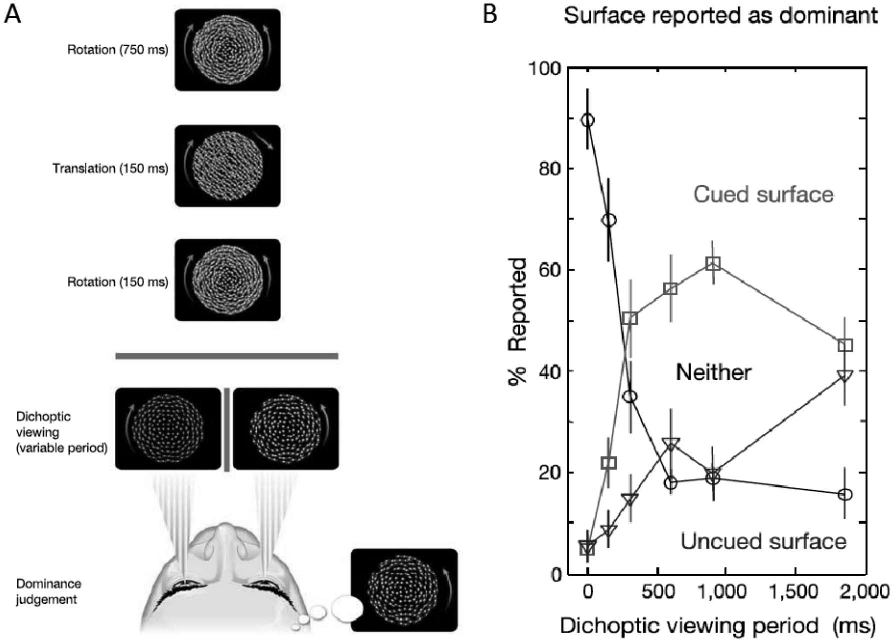


Figure 1.5.4. Influence of object-based attention on onset rivalry. Adapted from (J. F. Mitchell, Stoner, & Reynolds, 2004)
The onset of rivalry between dichoptic surfaces rotating in opposite directions is be systematically bias by exogenously attracting object-based attention to one of the rivalring stimuli (brief translation of one of the transparent surfaces) before the instigation of rivalry (Panel A). The first coherent percept, following a brief period of fusion, is most of the time in favour of the cued surface (Panel B).

1.5.3. Is attention necessary for binocular rivalry?

What happens if attention is diverted from the rivalring images? Would alternations occur anyways? Several studies have addressed this issue, starting from the influential paper by Ooi and He (1999) mentioned above: in the last experiment the authors showed that the onset of rivalry was severely affected if attention was divided in a dual-task paradigm (concomitant Vernier task), but even if alternations under divided-attention condition occurred less frequently, binocular rivalry was not abolished (Ooi & He, 1999). A similar conclusion was drawn by Paffen, Alais and Verstraten (2006), that, testing sustained alternations during prolonged rivalry showed that (as discussed above) performing a motion detection task did not stop perceptual alternations, bus slowed them down (Paffen, Alais, & Verstraten, 2006). Moreover, by increasing the number of rivalring images across the visual field, distributing therefore spatial attention to several targets, Paffen and Hooge (2011) also reported a reduction of alternation rate, confirming that dividing attention during binocular rivalry slows alternations but does not abolish them (Paffen, Hooge, Benjamins, & Hogendoorn, 2011). Interestingly, the same result is observed when attention is cross-modally diverted from the rivalring images: attending to an auditory stimulus in fact has been found to slow alternation rate in a similar way compared to intra-modal attentional division (Alais, van Boxtel, Parker, & van Ee, 2010).

All the studies mentioned above performed a dual task in which attention was divided between reporting binocular rivalry alternations and a concurrent task, so, even if attention was diverted from the rivalring visual stimuli, observers still had to track alternations, allocating therefore some attentional resources to the rivalring display. Recently, two clever studies have demonstrated that binocular rivalry is abolished if attention is totally diverted from the visual stimuli (i.e. observers are not required to track dominance and only attend to the concurrent task). Using the frequency-tagging SSVEP technique proposed by Brown and Norcia (Brown & Norcia, 1997) that allows to precisely track perceptual alternations from the EEG signal (Brown & Norcia, 1997), Zhang et al (2011) showed that when attention was diverted from the rivalring stimuli, alternations stopped and the EEG signal was similar to that obtained with a combination of the two stimuli, strongly pointing to the elimination of rivalry provoked by removal of attention (Zhang, Jamison, Engel, He, & He, 2011).

That attention is fundamental for binocular rivalry has been recently confirmed by psychophysical evidence: Brascamp and Blake (2012) invented a new experimental paradigm in which observers' rivalrous perception could be predicted, so that during the attentional task concomitant to binocular rivalry, rivalrous alternations tracking was not necessary. To increase the degree of rivalrous perception predictability, the authors took advantage of the phenomenon of "flash suppression" (Wolfe, 1984), in which the onset of rivalry can be controlled by the prior presentation of one of the two rivalring images, leaving unaltered the subsequent alternation process. Brascamp and Blake (2012) confronted conditions in which visual perception during binocular rivalry was reported by the observers (attended rivalry) and conditions in which attention was diverted to a RSVP task and fusable grating were presented (absent rivalry) with conditions where attention was diverted to the RSVP task (unattended rivalry), but rivalring stimuli were presented.

The experimental paradigm is illustrated in Figure 1.5.5.A: every trial was composed of three phases, the first phase was identical for all conditions and consisted of 2 seconds monocular presentation of one of the rivalring stimuli that will produce the phenomenon of flash suppression in which at the onset of rivalry the other visual stimulus will be perceived most of the times. The second phase varied between conditions, in the attended and unattended condition the rivalring gratings and a sequence of letters for a RSVP task were presented simultaneously for 2 seconds, in the attended condition observers were asked to ignore the letters and report their rivalrous visual perception while in the unattended condition they were asked to ignore the rivalring gratings and perform the RSVP task. The absent condition was similar to the unattended one, but instead of orthogonal gratings fusable gratings were presented. The third phase was identical for all conditions: only the rivalring grating were presented and observers were asked to report which one dominated.

Results are shown in Figure 1.5.5.B In the attended condition, as expected, during phase two visual perception was biased towards the visual stimulus forced by flash suppression, during phase three an echo of flash suppression was observed with a rebound in favour of the forced stimulus after a period of dominance of the other one. This result can be considered as a hallmark of rivalry. In the absent condition, during phase three no echo of flash suppression was observed and the trace was flat at chance level, this result constitutes instead the hallmark of no-rivalry. Interestingly, visual perception after the attentional task in the unattended rivalry condition did not show the echo of flash suppression and was comparable to the absent rivalry condition in which during the RSVP task visual stimuli were fusable gratings (Figure 1.5.5.B). From this result the authors concluded that binocular rivalry does not occur in the absence of attention.

That binocular rivalry does not occur in the absence of attention is a controversial result, for it disclaims the evidence that binocular rivalry is mediated by adaptation and early reciprocal inhibition between monocular representations of the visual stimuli (Alais, Cass, O'Shea, & Blake, 2010), that is supposed to be a low-level, automatic process and needs further investigation. The experimental evidence reviewed above nevertheless indicate that selective attention and bistable perception are strictly linked and that attention can modulate visual rivalrous perception, when dealing with a binocular rivalry experiment the role of attention therefore needs to be taken seriously into account.

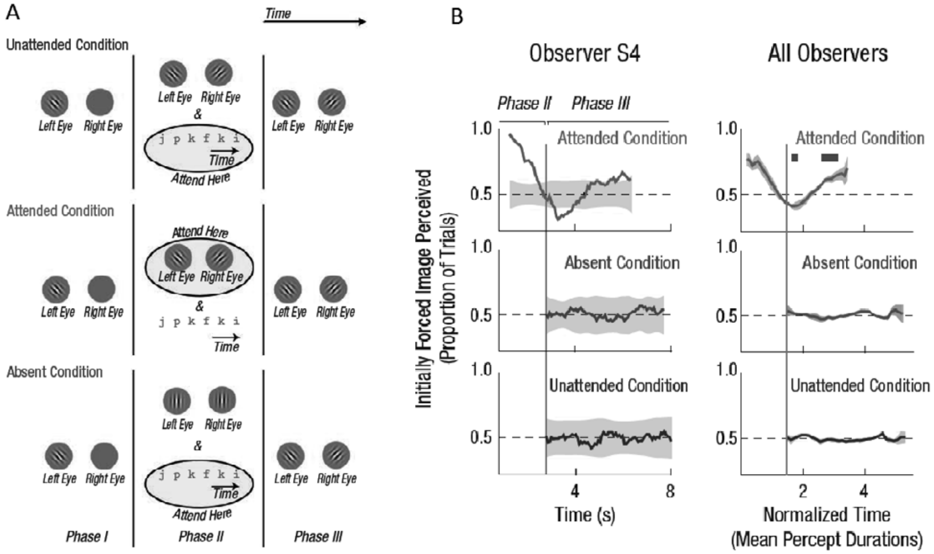


Figure 1.5.5. inattention abolishes binocular rivalry, psychophysical evidence. Adapted from (Brascamp & Blake, 2012).
Panel A shows a diagram of the different experimental conditions. In Panel B the average proportion of times in which the visual stimulus forced by flash suppression was perceived is reported as a function of time from the onset of phase two for the attended condition and from the onset of phase three for the other two conditions. In the unattended condition, the average proportion of dominance was flat at chance, with no echoes of flash suppression.

Chapter 2
Cross-modal interactions during binocular rivalry

2.1. Introduction. Multisensory Processing.

Robust perception of the external world is achieved by combining information arising from different sensory modalities (including vision, audition and touch), for none of them alone can provide information that is reliable enough for all the different properties of the external world. Integrating multisensory information is therefore a strategy that improves the quality of perception, allowing efficient interaction with the environment in all circumstances (Ernst & Bulthoff, 2004). In this light, it is surprising that until recently, sensory research focused mainly on the single sensory modalities independently. The blooming of research on multisensory processing has in fact occurred during the last decade, challenging the traditional principles that held before. The classic approach to multisensory processing relied on the assumption that sensory information was first analyzed by the unisensory areas, and then combined at a later stage (that was considered the "binding problem", Treisman & Gelade, 1980; von der Malsburg, 1999), in higher level cerebral areas that were therefore named "polysensory areas" (Benevento, Fallon, Davis, & Rezak, 1977; Felleman & Van Essen, 1991; Jones & Powell, 1970). In the next paragraphs we will review some of the most important studies that have recast multisensory research in a different light.

2.1.1. Multisensory processing in the superior colliculus (SC).

The recent explosion of research on multisensory processing is due to the advance in comprehension of the neural mechanisms underlying unisensory processing and to the pioneering work by Meredith and Stein (1983), who reported the existence of multisensory neurons (i.e. neurons responding to inputs from more than one sensory modality) in the deep layers of the superior colliculus (SC) of cats (Meredith & Stein, 1983). This finding pointed out the importance of multisensory combination to increase the probability of detecting and identifying objects in the external world. The superior colliculus in fact is a subcortical structure that plays a leading role in orienting behaviours such as directing the gaze to an object of interest. The receptive fields of multisensory collicular neurons encode the external space according to "spatiotopic coordinates", resulting in functional maps of the external environment in which multiple receptive fields (one for each sensory modality) overlap and respond to a particular region of the external space (Meredith & Stein, 1990).

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In different experiments, Meredith and Stein showed that, in order to elicit a response of the multisensory neuron in the SC, the signals from the different sensory modalities need to be aligned both in space (Meredith & Stein, 1986, , 1996) and in time (Meredith, Nemitz, & Stein, 1987). These constraints ensure that multisensory integration occurs only between signals representing the same object. Interestingly, when spatio-temporally congruent stimuli are presented in different sensory modalities, the multisensory neurons of the SC show a peculiar non-linear behaviour in their response. For example, when the unisensory inputs are weak, the response of the multisensory neurons is greater than the sum of the individual signals (Meredith & Stein, 1996). This response enhancement behaviour is named “superadditivity” and has been considered as a physiological benchmark of multisensory integration. Superadditivity is functionally important, for it ensures the detection of otherwise weak stimuli that would not be detected on their own but could be behaviourally salient. In line with this interpretation, superadditivity has been shown to be more likely to be found as the strength of the unisensory inputs decreases, a principle called “inverse effectiveness” (Stanford, Quessy, & Stein, 2005; B. E. Stein & Stanford, 2008). Both superadditivity and inverse-effectiveness are illustrated in figure 2.1.1. (reported from Stein & Stanford, 2008).

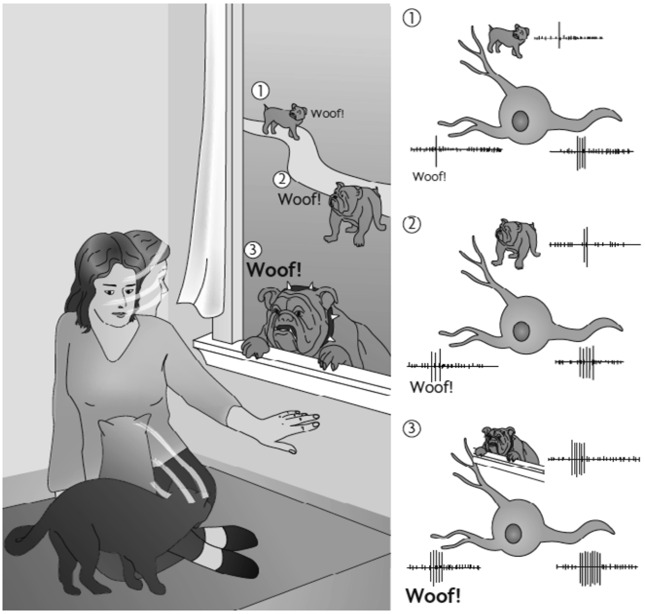


Figure 2.1.1. Non-linear characteristics of multisensory integration improve detection. Adapted from (B. E. Stein & Stanford, 2008).
The orienting behaviour of a woman and a cat to the approach of a dog based on vision and audition: when the dog is far (1), the visual and auditory signals associated with the dog are weak, but response of the collicular multisensory neuron is stronger than the sum of the unisensory components (superadditivity). As the dog approaches, the unisensory signals become stronger and multisensory response decreases proportionally, becoming additive (2) and subadditive (3) for vigorous unisensory signals. In this latter case the multisensory response is still stronger than the most vigourous unisensory signal, still improving detection of the dog.

As opposed to superadditivity, response depression of multisensory neurons has been observed for stimuli misaligned in space (Meredith & Stein, 1996), a mechanism that ihnhibits multisensory integration of objects occupying spatially separated positions. Taken together, the physiological properties of multisensory neurons guarantee fast and accurate orienting behaviours in response of congruent multisensory stimuli and slower and less accurate reactions for incongruent multisensory stimuli. Therefore, multisensory integration provides an advantage by improving the effectiveness of the interaction with the external world and, possibly, the survival of the organism, by enhancing detection of objects of interest or potential threats.

2.1.2. Multisensory Integration in temporal and parietal cortical areas.

Moving from a low-level structure of the midbrain, such as the superior colliculus, to the cerebral cortex, the properties of multisensory responses show different behaviours. For example, contrary to the SC, superadditivity seems to represent an exception rather than the rule for multisensory responses of cortical neurons. Superadditivity is an ideal characteristic for the guidance of orienting behaviours (that are the main function of the SC), for it enhances responses to regions of the external space showing spatio-temporal coincidence. Most cortical multisensory areas, instead have more complex functions, related to action, language, learning or even social perception (Campanella & Belin, 2007) and are therefore likely to encode coherent objects and semantic information. Congruency of multisensory input is therefore the most important feature for cortical neuronal population representing multisensory objects, more than needing a response enhancement to improve object detection and response speed to weak stimuli.

Neurons having overlapping receptive fields from different sensory modalities have been found in the anterior ectosylvian sulcus of the cat (Wallace, Meredith, & Stein, 1992), these multisensory neurons have larger receptive fields responding to congruent stimuli and only a few of them shows non-linear response patterns compared to the SC (Stein & Wallace, 1996). In the primate brain, research has focused mainly on posterior parietal cortex (PPC) and on superior temporal areas. PPC is a structure involved in attention and goal directed behaviours, such as reaching and gaze direction. Multisensory spatial maps found in PPC are encoded in coordinate frames that are common for the different sensory modalities (Avillac, Deneve, Olivier, Pouget, & Duhamel, 2005) and that dynamically realign with changes in gaze direction (Y. E. Cohen, Batista, & Andersen, 2002). Only one study found non-linear responses of neurons of a particular region of primate PPC: neurons in the ventral part of the intra-parietal sulcus (VIP) respond to spatio-temporally coincident visual and tactile stimuli and show both super- and sub-additive behaviours (Avillac, Ben Hamed, & Duhamel, 2007).

Superior temporal areas processing multisensory stimuli have been found in humans using neuroimaging techniques, such as fMRI. Most of those studies have failed in finding activations strong enough to be considered super-addictive, but have nevertheless reported reliable modulations of BOLD responses to multisensory stimuli (Beauchamp, Lee, Argall, & Martin, 2004; Beauchamp, Yasar, Frye, & Ro, 2008; Hein et al., 2007; van Atteveldt, Formisano, Blomert, & Goebel, 2007). Only a couple of studies have shown super-addictive BOLD responses, for example, Foxe et al (2002) have demonstrated superadditivity in the superior temporal gyrus of humans in response to audio-tactile stimuli (Foxe et al., 2002) and Calvert, Campbell and Brammer (2000) have found super-addictive responses to synchronized audio-visual speech in the left superior temporal sulcus (Calvert, Campbell, & Brammer, 2000). The only fMRI study that varied the intensity of auditory and visual stimuli in order to investigate the principle of "inverse effectiveness" in human superior temporal sulcus, found super-addictive modulation of the BOLD signal for weak stimuli representing simultaneous speech (Stevenson & James, 2009).

2.1.3. Cross-modal interactions in (previously thought) unisensory areas.

Experimental evidence listed in the previous paragraph, confirms the traditional view that considered multisensory integration as a process occurring at high levels of analysis (temporal and parietal areas) only after the accomplishment of unisensory processing. During the last decade this view has been challenged, with growing evidence showing a role of those that were believed to be unisensory areas and even primary sensory areas in multisensory processing. The growing number of cerebral areas showing multisensory properties has brought some authors to the provocative proposal of considering the whole cortex as multisensory and not as a set of separate areas specialized for a sensory modality (Ghazanfar & Schroeder, 2006).

One early study by Calvert et al (1997) showed the activation (BOLD) of auditory areas in response to lipreading in absence of sound, activation that was demonstrated to be specific for visual lipreading of speech and not for generic facial expressions or lip movements (Calvert et al., 1997). In the same year, Sathian et al (1997), using PET, showed an activation of visual extrastriate areas during a tactile task involving spatial frequency discrimination of grooved gratings (Sathian, Zangaladze, Hoffman, & Grafton, 1997). Two years later, the same group (Zangaladze, Epstein, Grafton, & Sathian, 1999) also demonstrated that the visual activity elicited by tactile stimulation was not an epiphenomenon, but was actually useful for the performance of the tactile task. Inhibiting the PET-defined visual area that was activated during the tactile task through transcranial magnetic stimulation (TMS) impaired observer's performance in the tactile spatial frequency discrimination task (Zangaladze, Epstein, Grafton, & Sathian, 1999). More recently, the primary visual cortex has been shown to be recruited for tactile stimulation after prolonged practice in a tactile task in expert Mah-Jong players (Saito, Okada, Honda, Yonekura, & Sadato, 2006) and a combination of activation and deactivation in early visual areas (BOLD modulation) has been shown (Merabet et al., 2007) during tactile stimulation (exploration of raised-dots patterns). Single-units recordings in monkeys have also revealed the existence of audiovisual (Ghazanfar, Maier, Hoffman, & Logothetis, 2005) and audio-somatosensory (Fu et al., 2003; Schroeder et al., 2001) interactions in the auditory cortex.

More insight about cross-sensory interactions in early sensory areas has been obtained by investigating the consequences of sensory deprivation. In fact, primary visual cortex of early blinds is activated during auditory (Kujala et al., 1995), tactile (Goyal, Hansen, & Blakemore, 2006; Sadato et al., 1996) and verbal tasks (Amedi, Raz, Pianka, Malach, & Zohary, 2003; Burton, Snyder, Diamond, & Raichle, 2002) and similarly in the deaf primary auditory cortex is activated during visual tasks (Finney, Fine, & Dobkins, 2001). Interestingly, the activation of V1 during Braille character discrimination (Sadato et al., 1996) has been demonstrated to be also functionally relevant, for the disruption of this activity impairs recognition performance. A very unfortunate case reported by Hamilton et al (2000) revealed the importance of V1 activity in tactile perception of early blinds: following an ischemic stroke that provoked bilateral occipital lesions, a woman blind from birth that was a proficient Braille reader lost her capacity of recognizing Braille characters despite preserved somatosensory perception (Hamilton, Keenan, Catala, & Pascual-Leone, 2000). Similarly, Cohen et al (1997) demonstrated that transiently disrupting occipital activity in early blinds with TMS impaired their ability of discriminating Braille characters and embossed letters, as well as their general somatosensory perception (Cohen et al., 1997).

Occipital cross-modal plasticity following visual loss has been demonstrated to be functionally relevant also for higher order tasks, especially for linguistic processing. Amedi et al (2004) showed that transcranic magnetic stimulation of occipital cortex in blinds impaired their verbal abilities (Amedi, Floel, Knecht, Zohary, & Cohen, 2004), a result that corroborated the hypothesis of the authors that cross-modal plasticity following sensory loss reflected an expansion of ventral cortex activation to primary visual areas, with a particular region in the occipito-temporal cortex dedicated to object integration and semantic processing sending feedback to V1 (Amedi, Jacobson, Hendler, Malach, & Zohary, 2002; Amedi, Malach, Hendler, Peled, & Zohary, 2001). Coherently with this view, in another study, Amedi et al (2003) found a left lateralized activation of the occipital cortex of blind patients during verbal tasks, independently of the sensory modality, and even for retrieval from memory (Amedi, Raz, Pianka, Malach, & Zohary, 2003). The authors also demonstrated that the amplitude of the occipital modulation (BOLD) during the verbal task positively correlated with individual observers' verbal memory (Amedi, Raz, Pianka, Malach, & Zohary, 2003). Another group expanded these findings by showing that V1 activation of blind patients for speech analysis correlated with difficulty of the verbal task (Roder, Stock, Bien, Neville, & Rosler, 2002).

The experimental evidence listed above clearly demonstrates that plastic changes occur in the deafferented visual cortex of blind patients, that is recruited by other sensory modalities. How does this plasticity occur? Are the connections between auditory and somatosensory areas to V1 created ex novo or are they reinforced following sensory loss? To investigate this issue, Kauffman et al (2002) measured tactile performance in a Braille characters discrimination task in normally-sighted participants, before, during and after five days of blindfolding; the idea being that transient visual deprivation could unmask the somatosensory connections to the visual cortex. During the five days of blindfolding, a group of participants performed 2 hours of tactile training per day and two control group of non-blinfolded participants were also tested. After blindfolding, Kauffman et al (2002) found that tactile performance was significantly better for the blindfolded group independently of the tactile training (Kauffman, Theoret, & Pascual-Leone, 2002). The authors interpreted these results as evidence of existing somatosensory connections to visual cortex that are masked by the strong and reliable visual input in normally-sighted individuals.

The same group confirmed this result in a following experiment in which they repeated the blindfolding procedure (Figure 2.1.2A) and the tactile discrimination task, but they also performed fMRI scans during and after blindfolding (Merabet et al., 2008). Figure 2.1.2. reports the results of the study. As in the first study, blindfolded participants showed a better performance in the tactile discrimination task compared to non-blindfolded individuals after five days of visual deprivation. Interestingly, this improvement disappeared one day following re-exposure to normal vision, showing a reversible recruitment of visual cortex by touch once vision is restored. Merabet et al (2008) also found that the advance in Braille character discrimination gained during blindfolding was accompanied with an increase activation (BOLD) in primary visual cortex during tactile stimulation compared with the control group of non-blinfolded that underwent the same tactile training (Figure 2.1.2C). One day following blindfolding removal, the increase in V1 activity disappeared with the perceptual advantage (Figure 2.1.2D). As for blind patients, Merabet et al (2008) demonstrated that the recruitment of V1 by touch following blindfolding was functionally relevant, for inhibiting occipital cortex with repeated transcranial stimulation at 1Hz annulled the improvement in tactile discrimination gained by the blindfolded individuals at day 5 from the onset of deprivation (Figure 2.1.2B). From these results the authors concluded that the cross-modal plasticity observed in blind patients with V1 being recruited by other sensory modalities results from reinforcing pre-existing connections from somatosensory and auditory areas, connections that are present in the normally sighted, but are masked by the visual input.

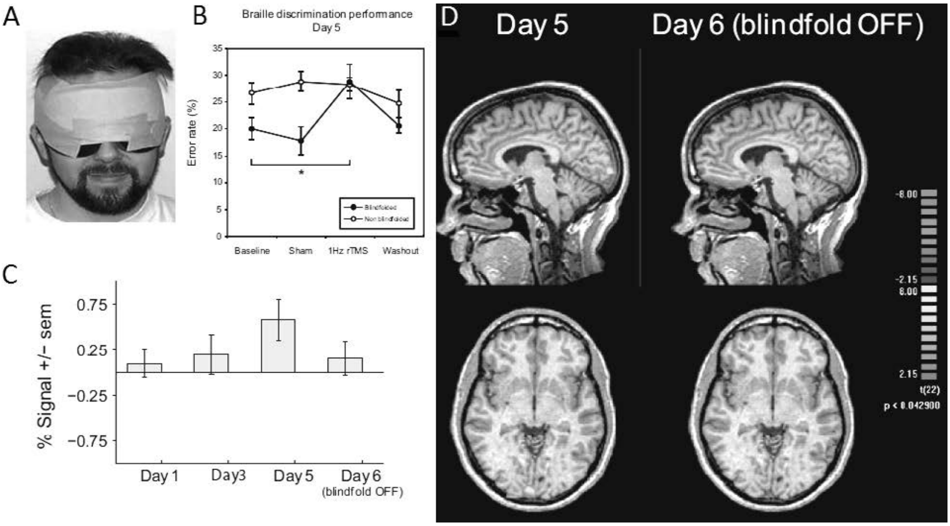


Figure 2.1.2. Rapid and reversible recruitment of early visual cortex by touch after 5 days of visual deprivation. Adapted from (Merabet et al., 2008).

Normal sighted individuals were blindfolded for five days (A) during which they underwent tactile training. Following blindfolding their performance to a Braille characters discrimination task significantly improved and concomitantly V1 activation (BOLD) increased during tactile stimulation compared with the non-blindfolded control group (C-D). V1 recruitment by touch was functionally relevant: when rTMS was delivered to occipital cortex the advantage in tactile discrimination was annulled (B). One day following re-exposure to normal vision their performance went back to that of non-blindfolded and the stronger activation of V1 disappeared (D).

That some connections to primary visual cortex from other sensory modalities exist has been confirmed by anatomical studies in the monkey brain. Using a back tracer from

V1, Falchier et al (2002) demonstrated the existence of connections from the belt and parabelt auditory cortices to the region of V1 representing the peripheral visual field (10-20°) and connection from the polisensory area of the temporal lobe (STP) to V1 (Falchier, Clavagnier, Barone, & Kennedy, 2002). The authors also showed that auditory connections to V1 were weaker than somatosensory ones and in a following study confirmed the existence of multisensory feedbacks to V1 (Clavagnier, Falchier, & Kennedy, 2004). The same result was obtained by Rockland and Ojima (2003) using anterograde tracers injected in parietal and auditory cortices (Rockland & Ojima, 2003).

2.1.4. Maximum Likelihood Estimation model of multisensory integration.

As pointed out in the previous paragraphs, integrating sensory signals from different modalities improves perceptual quality, for no single sensory signal can provide reliable information about the three-dimensional structure of the world in all circumstances. Multisensory integration therefore produces a gain of performance (Newell, Bulthoff, & Ernst, 2003). One of the most common models used to describe multisensory integration comes from the Bayesian probability theory and proposes that the brain combines information from different sensory modalities in a statistical optimal way, so that the combine outcome is the one that is more likely to be true. The Maximum Likelihood Estimation (MLE) model, first proposed by Ernst and Banks (2002) states that the combined estimate results from a linear sum of the various unisensory signals weighted by their reliability. That human multisensory perception matches the predictions of the MLE has been confirmed by many multisensory studies involving integration of visual, auditory and tactile cues (Alais & Burr, 2004; Bresciani, Dammeier, & Ernst, 2006; Ernst & Banks, 2002; Ernst & Bulthoff, 2004; Gepshtein & Banks, 2003; Gori, Del Viva, Sandini, & Burr, 2008; Gori, Mazzilli, Sandini, & Burr, 2011; Helbig & Ernst, 2007; Witten & Knudsen, 2005).

According to the MLE model if $\hat{S}_V$ is the estimate of an object property provided by vision and $\hat{S}_T$ is that provided by touch, the combined bimodal estimate $\hat{S}_B$ will result from the following formula: $\hat{S}_B = w_V\hat{S}_V + w_T\hat{S}_T$, where w_V is the weight assigned to the visual estimate and w_T that assigned to the tactile estimate. The weights represent the relative reliability (R_V and R_T) of the single sensory modalities that are combined in order to provide relevant information about the attribute of interest. So, for example the weight to be assigned to the visual estimate will be $w_V = R_V / (R_V + R_T)$, and vice versa for the tactile modality, so that the unimodal weights sum to one. The reliability of each sensory modality in the MLE model is defined as the inverse of the variability of the estimate provided by that modality, so $R_V = 1 / \sigma^2_V$. From this derives that the more reliable input is the less variable, so the input with the lowest variance will drive bimodal perception. The MLE model therefore allows not only the prediction of the mean bimodal estimate $\hat{S}_B$, but also the prediction of its variance σ^2_B: $1 / \sigma^2_B = 1 / \sigma^2_V + 1 / \sigma^2_T$. The precision of the optimally combined estimate is always higher than the highest precision of the unisensory estimates. This results in multisensory perception being more robust, for its variance is always lower than that of the individual sensory modalities (Ernst & Bulthoff, 2004). If one modality is more reliable than the other, the integrated estimate would be much closer to the more reliable within-modality estimate; this is the case of one modality "capturing" the other (Alais & Burr, 2004). The highest precise (the less variable) combined estimate occurs when the within-modality estimates are similarly reliable (Ernst & Banks, 2002).

A probabilistic approach to multisensory integration in which the multimodal combination occurs by weighting the different sensory modalities according to their reliability has a potential to explain the cross-modal effects observed before the proposal of the MLE model. For example, the MLE model agrees with the "modality appropriateness hypothesis" formulated by Welch and Warren (1980), according to which multisensory perception is dominated by the sensory modality with the highest sensitivity for the attribute of interest (Welch & Warren, 1980). This hypothesis was meant to explain the phenomena of "visual capture" (Bertelson & Aschersleben, 1998; Pavani, Spence, & Driver, 2000) for the spatial domain and that of "auditory capture" (Alais & Burr, 2003; Fendrich & Corballis, 2001; Morein-Zamir, Soto-Faraco, & Kingstone, 2003; Shams, Kamitani, & Shimojo, 2000) for the temporal domain. The MLE model explains these results by assigning a higher weight to the most reliable sensory modality, but it is a more flexible model for multisensory integration, for it predicts intermediate situations in which multimodal perception is dominated, but not entirely driven by the most reliable modality.

One of the most striking examples of MLE flexibility is the "reverse ventriloquism" demonstrated by Alais and Burr (2004). The ventriloquist effect is a well known multisensory illusion (Howard & Templeton, 1966) in which the perceived location of an auditory stimulus is captured by a simultaneous visual stimulus (Slutsky & Recanzone, 2001). Even if the auditory and visual stimuli are presented too far from each other to be perceived as arising from the same source, the perceived location of the auditory stimulus will nevertheless be attracted, even if not totally captured, towards the location of the visual stimulus (Bertelson & Aschersleben, 1998; Welch & Warren, 1980). Alais and Burr (2004) demonstrated that multisensory perception of the ventriloquist effect was well predicted by the MLE model (Alais & Burr, 2004) and that it could be reversed, with the auditory location capturing the visual one, by degrading the visual stimulus (blur), augmenting the variance of the visual estimate and decreasing therefore the reliability of the visual signal (Alais & Burr, 2004).

During the last decade, growing experimental evidence has shown that sensory modalities are often integrated in a fashion that closely approximates the predictions of the MLE, nevertheless, optimal multisensory integration does not occur indiscriminately: it is limited by spatial proximity (Gepshtein, Burge, Ernst, & Banks, 2005), by size congruency (Gepshtein & Banks, 2003) and by temporal coincidence (Bresciani et al., 2005; Shams, Kamitani, & Shimojo, 2000). In a few words, combination does not occur when signals from the different sensory modalities are not perceived as arising from the same source. Wallace et al. (2004) stressed the importance of perceived unity for multimodal fusion (Wallace et al., 2004). Bresciani et al (2006) found that subjects were able to integrate signals arising from different locations because they could see their hand touching the same object they were seeing. In this case, knowing that information came from the same object favoured the combination even though signals of the different modalities came from different spatial locations (Bresciani, Dammeier, & Ernst, 2006).

2.1.5. Cross-modal interactions and bistable perception

Multisensory integration can be a powerful strategy to resolve perceptual ambiguities arising from a single sensory modality. The MLE indeed predicts that combining multiple sources of sensory information is essential to achieve robust perception of the external world (Ernst & Bulthoff, 2004), disambiguating unreliable sensory information (e.g. noisy information). Bistable visual stimuli are intrinsically ambiguous and could therefore be a useful tool to reveal cross-modal interactions, for an unambiguous signal from a different sensory modality (audition, touch or olfaction) could help in disambiguating bistable visual perception that otherwise alternates between the two equally likely views. One early study on cross-modal disambiguation reported an interaction between sound and vision during the stream/bounce illusion, in which two disks oscillate across the screen travelling in opposite directions (antiphase), when the disks converge at the centre of the screen they are either perceived to bounce apart and move back to the starting position or to continue their original trajectory after a brief overlap. Sekuler et al (1997) showed that adding an auditory click at the time of the convergence of the two disks strongly biased the interpretation towards the bouncing percept, as if the two discs were impacting with each other (Sekuler, Sekuler, & Lau, 1997).

Several studies have reported audio-visual interactions during binocular rivalry. Kang and Blake (2005) demonstrated that binocular rivalry between a stationary grating and a grating flickering at 3Hz could be biased in favour of the flickering grating by introducing a sound amplitude-modulated in phase with the flickering grating (Kang & Blake, 2005). The sound lengthened dominance durations of the congruent visual stimulus, but did not affect its suppression (i.e. did not shorten phase durations of the incongruent visual stimulus). A similar result was recently obtained by Chen et al (2012) using auditory stimuli semantically congruent with one of the rivalring images. When the outlined drawings of a car and a bird were engaged in binocular rivalry, the concomitant presentation of a soundtrack semantically congruent with one of the images (for example the sound of birds singing), prolonged durations of that image, but did not shorten its suppression (Chen, Yeh, & Spence, 2012). In line with these results, audio-visual interactions between speech and Rubin's face-vase illusion has been shown to require conscious perception of the face producing the sound (Carter, Konkle, Wang, Hayward, & Moore, 2008).

One study showed that also suppression durations of the congruent rivalring stimulus can be influenced by auditory signals: by using random-dot kinetograms (RDKs) at different levels of motion coherence to create binocular rivalry between optic flows moving in opposite directions, Conrad et al (2010) showed that presenting a directional motion sound congruent with one or the other rivalring motion directions promoted dominance of the congruent visual stimulus both by prolonging its dominance durations and by curtailing its suppression (Conrad, Bartels, Kleiner, & Noppeney, 2010). That suppression of motion stimuli can be influenced by a congruent sound is consistent with the evidence that, as detailed in paragraph 1.2, motion signals can escape binocular rivalry suppression.

Somatosensory signals have also be shown to interact with bistable visual stimuli. Blake et al. (2004) used as visual stimulus the "kinetic depth effect", which occurs when viewing 2D parallel projections of a rotating 3D sphere, under these conditions perceptual reversals occur for opposite directions of rotation. Blake et al. (2004) demonstrated that touching an unambiguously rotating globe biased observers' perception in favour of the tactile rotation direction, by prolonging dominance of the congruent direction (Blake, Sobel, & James, 2004). Interestingly, they also demonstrated that pre-adaptation to a tactile direction did not bias perceived visual direction, indicating that the interaction between vision and touch only occurs for simultaneous bimodal stimulation (Blake, Sobel, & James, 2004). A similar result has been obtained using a visuo-haptic version of the Necker cube in which the visual interpretation congruent with the haptic configuration was favoured (Bruno, Jacomuzzi, Bertamini, & Meyer, 2007). Finally, vision and touch have been recently shown to reciprocal interact also during ambiguous motion perception in the motion quartet (Conrad, Vitello, & Noppeney, 2012), a form of perceptual bistability that engages visual as well as tactile rivalry (Carter, Konkle, Wang, Hayward, & Moore, 2008).

In addition to somatosensory information, active movement has been found to interfere with the dynamics of binocular rivalry Maruya, Yang and Blake showed that controlling the motion direction of one of the rivalring images with a voluntary action promoted the perception of the controlled visual stimulus both by prolonging its dominance and by curtailing its suppression (Maruya, Yang, & Blake, 2007). A result that is consistent with the survival of the suppressed signal along the dorsal pathway (see paragraph 1.2). Similarly, Hu and Knill (2010) recently reported that kinesthetic information provided by the arm movement can help in resolving visual ambiguity caused by the aperture problem (Hu & Knill, 2010).

Most cross-modal studies that have used bistable visual perception could be interpreted in principle as a shift of attention provoked by an unambiguous signal in another sensory modality. Most studies, in fact, have shown that cross-sensory stimulation can extend the dominance duration of the congruent rivalring stimulus, an effect that is similar of that of voluntary attention on binocular rivalry (Chong, Tadin, & Blake, 2005; Paffen & Alais, 2012). In line with this hypothesis, van Ee et al (van Ee, van Boxtel, Parker, & Alais, 2009) have demonstrated that cross-modal stimulation (either auditory or tactile) can enhance attentional control over binocular rivalry even though, in their paradigm, it was ineffective automatically and required a conscious attentional act to be effective (see paragraph 1.5.1. for details).

2.2. Touch interacts with binocular rivalry at early stages of visual processing.

As detailed in the previous paragraphs, growing evidence is challenging the classical view that considered multisensory convergence as occurring at high levels of processing in associative temporal and parietal areas only after that information from the different sensory modalities had been processed by the dedicated unisensory cortices. During the last decade, in fact, cross-modal interactions have been found at early stages of sensory processing, and even in primary sensory cortices that had always been thought to be purely unisensory.

We were interested in investigating whether touch could interact with vision at an early level of visual processing, for recruitment of primary visual cortex for tactile processing has been demonstrated in blind patients (Merabet et al., 2008; Sadato et al., 1996) and in normally sighted individuals after few days of visual deprivation (Merabet et al., 2008). Binocular rivalry is a powerful tool to investigate this issue. The intrinsic ambiguity of rivalrous visual perception creates ideal conditions to favour cross-modal interactions because disambiguation is thought to be one of the primary roles of cross-modal perception (Ernst & Bulthoff, 2004). Moreover, the temporary blindness to one image provoked by binocular rivalry suppression could unmask the somatosensory connections with early visual areas by weakening the visual signal through adaptation, added noise and mutual inhibition from the dominant stimulus

(Alais, Cass, O'Shea, & Blake, 2010). Finally, binocular rivalry suppression is thought to take place early in the visual system, attenuating neural activity related to the suppressed image from the earliest stages of visual analysis (LGN, Haynes, Deichmann, & Rees, 2005, monocular columns in V1, Tong & Engel, 2001) and completely destroying it at higher levels of visual processing (Tong, Nakayama, Vaughan, & Kanwisher, 1998), so that, if appropriate visual stimuli are used (for example oriented gratings), neural activity associated with the suppressed image is not traceable outside of V1 or V2. Observing an interference of the tactile signal with the suppressed visual stimulus will therefore point o an early locus of the cross-modal interaction.

In the next paragraphs we will present three studies in which we investigated the interaction between vision and touch during binocular rivalry. In the first study we showed that haptic exploration of an oriented grating promoted dominance of the parallel visual stimulus both by prolonging its dominance and by curtailing its suppression and that the interaction was strictly tuned for matched visuo-haptic spatial frequencies. In the second study, we confirmed the main effect of touch and we expanded the selectivity of the interaction for orientation. By performing a cross-sensory orientation discrimination experiment we also demonstrated that the sharp orientation tuning of the visuo-haptic interaction did not result from a conscious categorization, ruling also out the possibility of attention and response bias playing a leading role in mediating the interaction. In the last experiment, we showed that spatial proximity between the visual and the haptic stimulus is necessary to observe the interaction and that passive tactile stimulation is as effective as active haptic exploration in influencing the dynamics of binocular rivalry, showing as well the same selectivity for spatial frequency. Finally, we also found that simultaneous presentation of visual and haptic stimuli is crucial for cross-sensory interaction by showing that haptic stimulation does not prime the onset of rivalry.

2.2.1. Touch specifically interferes with the dynamics of binocular rivalry

When incompatible images are presented to corresponding retinal regions, interocular differences prevent the brain from achieving binocular fusion and normal binocular vision is not possible. Instead, the conflicting images trigger a continual struggle for visual awareness in which only one image is perceived at a time and the other is suppressed from awareness. These perceptual alternations, a form of bistable perception known as binocular rivalry (Alais & Blake, 2005; Levelt, 1965), will continue irregularly each second or two for as long as the conflicting stimuli are present. Because of the peculiar dissociation between a continuous physical stimulation but an alternating visual perception, binocular rivalry has been used as a tool to investigate the neural correlates of visual awareness and the resolution of perceptual ambiguity (Klink, van Wezel, & van Ee, 2012; Koch, 2007; Logothetis, 1998).

Binocular rivalry suppression takes place early, probably in V1 (Tong, Meng, & Blake, 2006). However, a trace of the suppressed signal has been detected along the dorsal visual pathway (BOLD responses, Fang & He, 2005) and demonstrated with psychophysical experiments. In line with the evidence of neural signals related to the suppressed visual stimulus surviving along the dorsal pathway, the suppressed image of a rotating sphere during rivalry is restored to consciousness when the observer actively controls the rotation (Maruya, Yang, & Blake, 2007) and a similar effect on the suppressed signal has been shown for motion perception (Andrews & Blakemore, 1999).

The resolution of perceptual ambiguity is in thought to be one of the main functions of cross-modal interactions (Ernst & Bulthoff, 2004; Klink, van Wezel, & van Ee, 2012), bistable perception is therefore a powerful tool to reveal an interference of another modality on vision. In this first experiment, that was published in 2010, we asked whether cross-modal sensory signals could selectively interact with rivalrous visual signals (oriented gratings) that are analyzed at a very early stage, probably V1.

2.2.1.1. Materials and Methods

Subjects

Seven subjects (all females) participated in the first experiment and six subjects (one male) participated in the second experiment in which we measured spatial frequency selectivity; all had normal or corrected to normal vision, normal stereo acuity (Frisby stereotest, Sasieni, 1978), and no strong eye dominance.

Apparatus and stimuli

The experiment took place in a dark and quiet room. Visual stimuli were generated by the ViSaGe (CRS, Cambridge Research Systems) housed in a PC (Dell) and controlled by Matlab programs. Stimuli were displayed on a 21" Sony GDM-F520 Trinitron colour monitor driven at a resolution of 1280x800 pixels, with a refresh rate of 120 Hz. Subjects' head position was stabilized by a neck-rest. They viewed the display at a distance of 40 cm through CRS Ferro-Magnetic shutter goggles that occluded alternately the two eyes at the same frequency as the refresh rate of the monitor. Responses were recorded through the computer keyboard. Visual stimuli were two Gabor Patches, oriented either vertically or horizontally (size: 1.5°, spatial frequency: 5 c/cm, corresponding to 3.5 cpd, contrast: 45%), presented on a grey background (luminance: 7.8 cd/m^2, C.I.E: 0.299 0.327) in central vision. Presentations were alternated at the same frequency as the shuttering goggles, so each eye was presented with only one of the two stimuli. The haptic stimulus was a 12.8 x 15 cm sinusoidally grooved Plexiglas, of the same spatial frequency as the visual stimuli (5 c/cm), positioned on a prop fixed on the table under the monitor. It could be rotated by the experimenter so that its orientation could be either vertical or horizontal, i.e. either parallel or orthogonal to the orientation of the visual percept. Subjects could see neither the Plexiglas nor their hand touching it; they had no visual feedback while reaching the stimuli. The main task of the subjects was to report by key-press their visual perception, horizontal or vertical. They rubbed their right thumb over the grooved Plexiglas; they were not asked to pay particular attention to it, but to consider that it was generated by the same object that was seen through the goggles (even though the two stimuli were presented at different spatial locations or provided conflicting information, a common practice in multisensory integration studies, e.g. Alais & Burr, 2004; Ernst & Banks, 2002; Gori, Del Viva, Sandini, & Burr, 2008).

For the second experiment that measured the spatial frequency selectivity of the effect, the visual stimuli were displayed on a 20-inch Clinton Monoray (Richardson Electronics Ltd., LaFox, IL) monochrome monitor (which has a fast phosphor and therefore less leakage between the eyes), driven at a resolution of 1024x600 pixels, with a refresh rate of 120 Hz. Visual stimuli were of 3 c/cm (corresponding to 1.6 cpd at a distance of 30 cm) or 1.3 c/cm (corresponding to 0.7 cpd) spatial frequency (background luminance: 37.4 cd/m^2, C.I.E: 0.442 0.537). Haptic stimuli were 4 sinusoidal gratings of different spatial frequencies (size: 3 cm, spatial frequencies: 1.3 c/cm, 2 c/cm, 3 c/cm, 4 c/cm) created with a 3D printer (Dimension Elite SST, Stratasys, Inc., Eden Prairie, MN), positioned on a touchscreen (Magic Touch, Keytec Inc., Richardson, TX), in order to record the timing of touch periods. Different spatial frequencies were presented in separate blocks in randomized order, following a preset table of random number generator.

Task and procedure

After a countdown, the visual stimuli appeared generating binocular rivalry (Levelt, 1965). Subjects reported their visual perception (vertical or horizontal) by continuously pressing with the left hand one of two keys (left or right arrows) of the computer keyboard. As assessed in pilot studies and in debriefing sessions, given the small size of the stimuli, mixed percepts occurred for very brief periods, only during perceptual transitions, and their frequency remained constant across conditions. During the observing period, at approximately regular intervals, subjects were asked to explore the haptic stimulus with the right thumb performing circular movements (in order to avoid a possible influence of the motor direction), until the experimenter gave a stop signal (each touch period had a mean duration of 3 s and a standard deviation of 0.7); touch periods were interleaved with no-touch (vision only) periods (mean duration 7.1 s, standard deviation 1.9 s). During no-touch periods, the experimenter changed the orientation of the Plexiglas, alternating the vertical and horizontal orientations following preset random generated sequences (the manoeuvre was invisible to the subjects and the orientation of the Plexiglas unpredictable at each touch period). Touch periods and Plexiglas orientation were recorded by the experimenter by continuously pressing the appropriate mouse button. In both experiments, sessions lasted 180 s and were divided in two parts; in the second part the orientation of the visual stimuli was swapped between the two eyes.

We also recorded pilot data where the duration of haptic stimulation was extended up to 3 minutes. The results indicated that the subjects had difficulty in keeping attention to the haptic stimulus, while attention is important in modulating binocular rivalry (Chong & Blake, 2006) and cross-modal interactions during it. Given the dynamics of the effect we chose the 3s interval that optimized the number of sampled touch periods for each recording session.

2.2.1.2. Results

We tested whether touch could interfere with the dynamics of binocular rivalry by having subjects explore haptically a grooved stimulus of the same orientation as one of the two rival visual stimuli. Visual stimuli were orthogonal Gabor Patches (oriented vertically or horizontally), displayed alternatively to the two eyes; the haptic stimulus was a sinusoidal grooved Plexiglas, matched in spatial frequency with the visual gratings; subjects could see neither their hand nor the stimulus they touched. While reporting the perceived orientation of the visual stimulus, participants were required at random intervals to touch (with circular movements of the right thumb, to avoid interference of movement direction) the haptic stimulus and to release it after a brief period of ~3 sec (short enough to avoid deployment of attention (van Ee, van Boxtel, Parker, & Alais, 2009) and adaptation to the haptic stimulus, but long enough to allow tracing its effect on the slow dynamic of binocular rivalry). For each touch period, visual and haptic stimuli were unpredictably parallel to each other or orthogonal (figure 2.2.1.1.A).

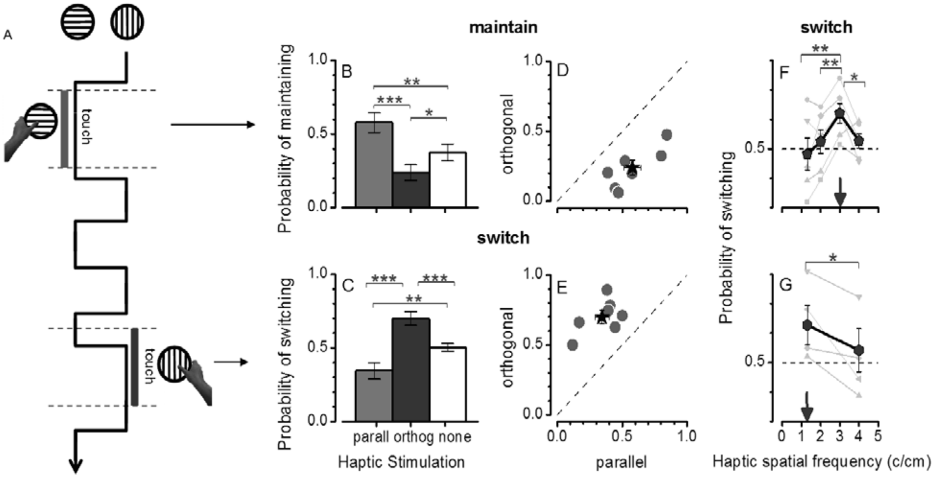


Figure 2.2.1.1. Experimental paradigm and main results.
The black line in Panel A represents the visual perception switching between dominance of the vertically and horizontally oriented visual stimulus. Two example touch periods are shown, the first beginning with parallel visuo-haptic stimulation and maintaining it for the whole touch period, the second beginning with orthogonal visuo-haptic stimulation and switching to parallel. The probability of maintaining dominance of a stimulus during the whole period (Panel B, ** refers to $p<0.01$, *** to $p<0.001$) was significantly greater for periods of congruent visuo-haptic stimulation (light grey bar), both compared to periods of incongruent stimulation (dark grey bar) and to no touch periods (white bar). Panel D shows individual subjects data: all circles lie beneath the graph bisector ($y < x$). On the other hand, the probability of switching perception (Panel C) was significantly greater during periods of orthogonal visuo-haptic stimulation both compared to periods of parallel stimulation and to no touch periods. Panel E shows individual subjects' data: the effect is consistent for all subject, all circles lie over the graph bisector ($y > x$). Panel F and G show the results of a spatial frequency selectivity experiment: the probability of switching perception when the touch period began with an orthogonal visual percept, is plotted as a function of the spatial frequency of the haptic stimuli (ranging from 1.3 c/cm to 4 c/cm). The arrow represents the visual spatial frequency tested. The effect peaks when visual and haptic spatial frequencies are matched. (* refers to $p<0.05$, ** to $p<0.01$).

During a touch period observers could either maintain in dominance the same visual stimulus for the whole touch period duration, or they could switch in favour of the other visual stimulus. We computed the probability of these two alternatives conditioned to the type of visuo-haptic stimulation (parallel, orthogonal or for periods of visual-only stimulation of comparable duration) and we found that the probability of maintaining or switching perception was importantly influenced by touch. Haptic stimulation disambiguated visual perception both by promoting dominance of the visual stimulus with the same orientation and by reducing suppression.

When the orientations of the haptic and visual stimuli were orthogonal, the probability of switching perception, re-establishing congruency of visual and haptic stimuli orientation, increased by 35% relative to periods of congruent visuo-haptic stimulation and by 20% relative to no touch periods (figure 2.2.1.1.C). This suggests that the haptic signal boosted the suppressed stimulus signal provoking a perceptual switch, leading the parallel stimulus to revert to perceptual dominance. Conversely, when haptic and visual stimuli were parallel, the probability of maintaining dominance of the visual stimulus during the whole period of haptic stimulation increased by 34% relative to periods of orthogonal visuo-haptic stimulation and by 20% relative to no touch periods (figure 2.2.1.1.B). Hence the duration of dominance as well as of the suppression of a rival visual stimulus can be substantially affected by the presentation of a congruent haptic stimulus. The individual data reported in Figures figure 2.2.1.1.D and figure 2.2.1.1.E show that the effect is consistently observed in all tested subjects.

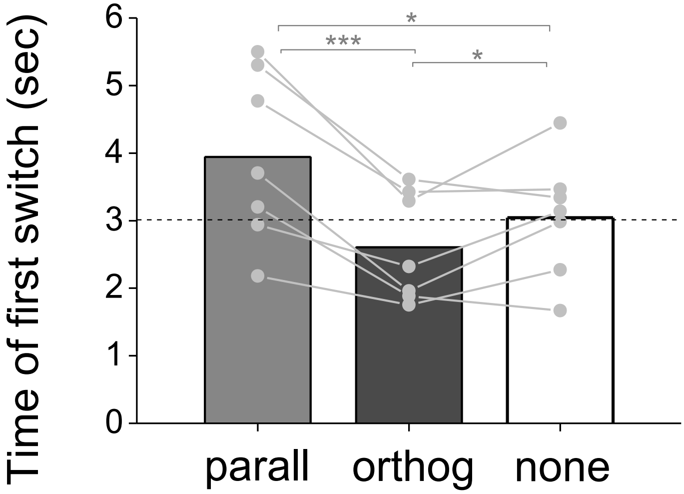


Figure 2.2.1.2. Effect of haptic stimulation on dominance durations.
The three bars show the time, averaged across subjects, of the first switch relative to the onset of a touch period for the three tested conditions: parallel (light grey), orthogonal (dark grey) visuo-haptic stimulation, or visual-only stimulation (white bar). The horizontal dashed line represents the average duration of touch periods (3.01 sec). The first switch occurred later for parallel visuo-haptic stimulation than for orthogonal visuo-haptic stimulation. The difference between these two values was statistically significant ($p<0.001$, three stars), as well as the difference between each one and the no-touch value ($p<0.05$, one star).

Since touch periods were delivered at random intervals during binocular rivalry viewing the onset of touch never coincided with the onset of a dominance phase, we could not compute mean phase durations of one or the other visual stimulus during haptic stimulation. In order to quantify the effect on dominance durations we therefore computed the time of the first switch following the onset of touch separately for touch periods in which haptic stimulation was parallel to the dominant visual stimulus, for periods in which the haptic orientation was orthogonal to the visual orientation and for no-touch periods. In agreement with the probability pattern, we found that haptic stimulation prolonged dominance duration of the parallel visual stimulus and curtailed dominance duration of the orthogonal visual stimulus compared to no-touch periods (figure 2.2.1.2.). For parallel visuo-haptic stimulation the first switch exceeded the offset of touch and occurred on average at 3.94±0.48 sec from touch onset. Vice versa, for orthogonal visuo-haptic stimulation the first switch occurred well before the offset of touch (mean time: 2.6±0.3 sec).

By repeating the experiment using visual and haptic stimuli of different spatial frequencies we found that the effect of touch on the suppressed visual stimulus was selective for matched visuo-haptic spatial frequencies. Figures 1 figure 2.2.1.1.F and figure 2.2.1.1.G show the modulation of the probability of switching perception from the orthogonal visual stimulus towards the haptic orientation as a function of the haptic spatial frequency for two different spatial frequencies of the visual stimuli. The probability peaks when the visual and the haptic stimuli have the same spatial frequency.

2.2.1.3. Discussion

Our results demonstrate that a visual stimulus, rendered invisible by binocular rivalry suppression, can nonetheless revert to consciousness when boosted by a concomitant haptic signal of congruent orientation and spatial frequency. When there is a conflict between the orientation of the visual and the haptic stimuli, vision switches to the congruent orientation, indicating that the system uses the haptic signal to resolve binocular rivalry. Touch and visual signals are optimally fused in many tasks (Hillis, Ernst, Banks, & Landy, 2002), but the fusion is not mandatory, consistent with the prevailing view that it is mediated by high-level associative multisensory cortex. In previous studies, for bistable visual signals, the haptic stimulus cannot modulate the suppressed phase (Blake, Sobel, & James, 2004) and active listening was required to increase the phase duration of the congruent visual stimulus (van Ee, van Boxtel, Parker, & Alais, 2009). However, the present results show that touch can make visible an otherwise unseen stimulus, suggesting mandatory fusion.

That touch influenced binocular rivalry both by prolonging dominance of the parallel visual stimulus and by shortening its suppression (i.e. shortening dominance of the orthogonal visual stimulus) was confirmed when we computed the time of the first switch from the onset of touch. This indicates that touch interferes with the suppressed oriented grating, shortening the suppressed phase and reverting the parallel orientation stimulus to dominance. Interestingly, several psychophysical (Freeman, Nguyen, & Alais, 2005) and neurophysiological (Tong, 2005) studies have shown that neural activity related to the suppressed visual stimulus is disrupted beyond V1. Suppression of oriented gratings during binocular rivalry takes places after orientation adaptation (Blake & Fox, 1974a) and orientation fusion (Pearson & Clifford, 2005a), two phenomena that are typical of V1 circuitry, while adaptation to more complex stimuli, like faces, is abolished during suppression (Moradi, Koch, & Shimojo, 2005). Nevertheless, a residual trace of the suppressed stimulus can be detected beyond V1.

With one exception (Sterzer, Jalkanen, & Rees, 2009), evidence suggests that such residual activities occur along the dorsal pathway (Fang & He, 2005) which is known to mediate action rather than conscious perception (Goodale & Milner, 1992). This residual trace may interact with visible signals. Using plaid motion stimuli, it has been shown that the suppressed signal changes the perceived direction of motion (Alais & Parker, 2006; Andrews & Blakemore, 1999) and the reflexive eye movement associated with it (Spering, Pomplun, & Carrasco, 2009). Interestingly, in a different context where binocular rivalry was not involved, a non informative tactile stimulus was shown to make detectable an otherwise under-threshold visual stimulus (Arabzadeh, Clifford, & Harris, 2008). These evidences, together with the spatial frequency selectivity of the effect on the suppressed signal reported here and in the main text, strongly suggest that touch of simple oriented gratings interact with vision at early level, probably at V1, in agreement with recent neurophysiological data (Ghazanfar & Schroeder, 2006).

In principle, the effect could be mediated by attention or imagination. However, the spatial frequency selectivity of the observed effect (with the peak effect changing with the spatial frequency of the visual stimulus) is inconsistent with attentive or other non-specific effects, and points strongly to early interactions between haptic and visual signals. V1 neurons have the narrowest spatial frequency tuning of visual neurons and could mediate the effect reported here, which requires a bandwidth of less than 1 octave.

Few factors decrease suppression of a rival stimulus: only contrast or, to a much lesser degree, attention (Paffen, Alais, & Verstraten, 2006). Interestingly, both the contrast of the stimulus and attention are known to modulate primary visual cortex activity. In order to boost a suppressed visual signal, therefore, it is very likely that the haptic signal must reach early visual cortex, in line with previous evidence from blind patients, in which V1 is recruited for tactile processing (Pascual-Leone, Amedi, Fregni, & Merabet, 2005). It has recently been proposed that reorganization of the visual cortex in the blind reinforces pre-existing connections between somatosensory and visual cortex, the tactile input to visual cortex being normally masked by the robust visual input. In the absence of visual inputs (for example during prolonged blindfolding (Pascual-Leone, Amedi, Fregni, & Merabet, 2005)), these connections become more effective. We propose that the same happens during binocular rivalry suppression, revealing the non-visual roles of the occipital cortex by unmasking tactile inputs. Our findings strongly suggest that not only can haptic signals modulate activity at the earliest stages of visual processing (consistent with recent neurophysiological evidence, see Supplemental References), but that these signals influence low level visual perception opening the way to consciousness for an otherwise invisible stimulus.

2.2.2. The interaction between vision and touch during binocular rivalry is strictly tuned for orientation

In our previous experiment (Lunghi, Binda, & Morrone, 2010) we have shown that touching an oriented haptic grating congruent with one or the other rivaling images extended the dominance duration of the parallel visual stimulus. In addition, and unlike the effects of attention on rivalry, we have demonstrated that the tactile signal shortened the period of suppression of the congruent visual signal and restored it more quickly to consciousness than in a visual-only condition. This implies that the tactile signal interacts with the congruent visual signal outside of awareness (i.e., while it is suppressed). We have also shown that the influence of haptic stimulation on the dynamics of binocular rivalry was tuned for spatial frequency in that visual and tactile gratings with the same spatial frequency produced an effect whereas a difference of one octave eliminated it. From these observations (haptic interaction during suppression and spatial frequency tuning), and given that neural signals associated with the suppressed image are not traceable outside of V1-V2 (Blake & Logothetis, 2002; Lin & He, 2009) and that neurons with narrow spatial tunings are only found in primary visual cortex (Maffei & Fiorentini, 1973), we interpreted our data as evidence of an early, compulsory interaction between vision and touch.

The conclusion that vision and touch interact early in visual processing squares with other recent evidence. Multisensory convergence in primary visual cortex has been found in the macaque brain (Falchier, Clavagnier, Barone, & Kennedy, 2002), and recently the primary visual cortex of rodents has been shown to respond to tactile exploration of novel objects (Vasconcelos et al., 2011), its response correlating with the animal's performance in a tactile aperture discrimination task. In humans, V1 activity (BOLD) has been found in response to tactile stimulation (Merabet et al., 2007), moreover, the primary visual cortex is recruited for tactile processing both in blind patients (Sadato et al., 1996) and in blindfolded normal-sighted adults (Merabet et al., 2008). The early visual-touch interaction fits with recent evidence of multisensory convergence and with a proposal that the whole brain is fundamentally multisensory, including areas traditionally thought of as primary sensory cortices (Ghazanfar & Schroeder, 2006).

During our visiting period at the School of Psychology of the University of Sydney, we have further investigated the hypothesized early interaction between vision and touch during binocular rivalry by testing whether it is specific for another basic property of the primary visual cortex, *orientation selectivity* (Hubel, Wiesel, & Stryker, 1977). Using the same paradigm as the first experiment, we confirmed that the effect of congruent touch in binocular rivalry acts in two ways, both extending the dominance duration of the visible stimulus and reducing the time that the invisible stimulus is suppressed. Importantly, by varying the relative orientation of the visual and tactile gratings, we show that this effect of touch on vision is strictly orientation tuned, reinforcing the hypothesis that the interaction occurs at the earliest stages of visual analysis, probably V1.

2.2.2.1. Materials and Methods

Subjects

Eight subjects (four males, average age 28.3±7.3 years), including the authors, participated in the main experiment (subject JT took part in only five conditions) and five subjects from this group also participated in the orientation discrimination experiment; all had normal or corrected-to-normal vision and no strong eye preference.

Ethics Statement

Participants gave written informed consent. The experimental procedure conformed to the declaration of Helsinki and was approved by the local ethics committee (Human Research Ethics Committee (HREC) Low Risk Executive Committee, University of Sydney, Protocol No. 14893).

Apparatus and Stimuli

The experiment took place in a dark, quiet room. Visual stimuli were created in MATLAB using PsychToolbox (Brainard, 1997), and displayed on a 17-inch LCD monitor (Hp 1702), driven at a resolution of 1280x1024 pixels with 60 Hz refresh rate . Observers viewed the visual stimuli through a mirror stereoscope placed 40 cm from the monitor. In the main experiment responses were recorded through the computer keyboard, in the cross-modal orientation discrimination responses were also recorded through a pedal switch. Visual stimuli were two oblique orthogonal achromatic gratings (orientation: ±45°, size: 2.5 cm, spatial frequency 2 cyc/cm, contrast 20%, mean luminance 48 cd/m^2), surrounded by a white smoothed circle included in a white squared frame (size 3.6 cm) to facilitate binocular fusion, presented on a black uniform background (luminance 0.28 cd/m^2) in central vision. The tactile stimulus was a sinusoidal grating (size: 3 cm, spatial frequency 2 cyc/cm) created with a 3D printer (a diagram of the experimental setup is reported in Figure 2.2.2.1A). Participants could not see their hand or the tactile stimulus during the experiment. The tactile grating was attached to a shaft and its orientation could be precisely varied by the experimenter using a calibrated switch.

Task and Procedure

Binocular Rivalry

The dynamics of binocular rivalry can be influenced by haptic signals, as previously documented (Lunghi, Binda, & Morrone, 2010). Here we investigate the orientation tuning of this effect of touch on vision during binocular rivalry. Using the same experimental paradigm as Lunghi et al (Lunghi, Binda, & Morrone, 2010), we varied the orientation of the haptic stimuli in different experimental blocks, introducing a mismatch in orientation with the visual stimuli ranging from ±7.5° to ±30°.

Each observer participated in five 180-sec experimental sessions x seven experimental conditions for a total time of 105 minutes, over different days. Seven different haptic conditions in which a mismatch in orientation between the visual and haptic stimuli was introduced were tested in separate blocks. Within every block two orthogonal haptic orientations were tested, one clockwise, the other counterclockwise relative to vertical. The mismatch in orientation was defined as the difference between the orientation of the visual gratings (±45°) and the haptic gratings whose orientation could be: -30°, -15°, -7.5°, 0°, +7.5°, +15°, or +30° relative to the orientation of the visual. The order of the different conditions was randomized for every observer. The two haptic gratings in a block were always orthogonal to each other. Within each block, this grating pair was rotated by a fixed amount relative to the visual gratings, so that one haptic grating was offset by that amount relative to one visual grating and the other haptic grating was offset by the same amount relative to the other visual grating.

Observers were given time to adjust the stereoscope in order to achieve perfect binocular fusion at the beginning of every experimental block when only the square frames were presented. When ready, observers pressed a key and after an acoustic signal (beep) the visual stimuli appeared. Participants were instructed to report their rivalry fluctuations by indicating continuously which visual orientation (clockwise or counterclockwise) they perceived. They did so by pressing one of two keys on the computer keyboard. With the small stimuli we used, the rivalry percepts in our experiment were generally coherent and unitary, with mixed perception occurring only briefly at the time of percept transitions. At the end of each experimental session the orientation of the rival stimuli were swapped between the eyes to counterbalance any eye dominance effects.

During the 3-minute trials, at approximately regular intervals, observers were asked to explore the haptic stimulus with their right thumb by performing a constant translational movement, until the experimenter gave a stop signal (average touch period: 2.65±0.18 s). The experimenter manipulated the orientation of the haptic stimulus between each touch period by alternating between orthogonal orientations (clockwise or counterclockwise) according to a pre-computed random sequence so that the haptic orientation was unpredictable. A cartoon of the experimental paradigm is reported in Figure 1B. Touch periods were brief to avoid haptic adaptation and maintain the haptic stimulation salient. Touch periods were compared to no-touch control periods. Since the effect of haptic stimulation takes more than 1 second to recover after the offset of touch, we defined the no-touch control periods as starting 1.8 seconds after the offset of touch and matched their duration to that of the touch periods (i.e., 2.65 s).

Cross-modal orientation discrimination

In order to evaluate if observers were aware of the orientation mismatch between the visual and the haptic stimuli we ran a cross-modal orientation discrimination experiment. During simulated binocular rivalry, we varied the orientation difference between the visual and the haptic stimuli and asked observers to judge whether the visual and the haptic stimuli had the same orientation or not.

As in the rivalry experiment, observers in the orientation discrimination experiment were given time to adjust the stereoscope in order to achieve perfect binocular fusion at the beginning of every experimental block. When ready, observers initiated the trial sequence with a key-press and the visual stimuli appeared. Binocular rivalry was simulated by binocularly presenting iso-oriented gratings (either +45° or -45° relative to vertical) for durations randomly varying between 2 and 3.5 seconds. To simulate the brief patchwork of gratings often perceived during dominance transitions both orthogonally oriented gratings (+45° and -45°, Guzman-Martinez, Ortega, Grabowecky, Mossbridge, & Suzuki, 2012a) were presented for a short random duration of 0.5-0.7 s. All transitions from one grating to patchwork to the other grating were temporally smoothed and observers were not told that it was a rivalry simulation and in debriefing sessions none of them reported noticing it was a rivalry mimic condition. Observers tracked their visual perception by continuous key-press as in the first experiment. At approximately regular intervals observers were asked to explore with their right thumb the haptic stimulus that in a given each touch period could have either the same orientation as the visual stimuli (+45° or -45°) or could be mismatched by -7.5°, -15°, +7.5° or +15° relative to the visual stimulus. All clockwise and all counterclockwise haptic orientations were tested in separate blocks. During the touch period (mean touch duration 2.1±1.1 s), observers were required to indicate whether the haptic stimulus was further clockwise or further counterclockwise relative to the visual stimulus, and they did so by pressing the appropriate pedal on a two-pedal floor switch. Only responses registered during the touch period were considered for analysis, meaning in effect that observers had to make their response within about 2 seconds of commencing their touch exploration. In order to validly compare discrimination of the visual-haptic orientation difference across conditions, we considered for analyses only haptic orientations that were tilted "further clockwise" than the visual orientation. This was because performance for the 0° visual-haptic difference showed a bias towards clockwise responses which would spuriously exaggerate differences with haptic gratings tilted counterclockwise. Observers' performance for haptic orientations tilted "further counterclockwise" did not statistically differ from performances for "further clockwise orientations".

2.2.2.2. Results

Observers reported binocular rivalry alternations between orthogonal gratings while periodically exploring an adjacent haptic grating (Figure 2.2.2.1A) which was randomly varied by the experimenter to be either parallel or orthogonal to the visual stimulus dominating the observer's perception at that time (Figure 2.2.2.1B). During a touch period observers could either maintain the same visual percept or switch perception in favour of the previously suppressed visual stimulus (Figure 2.2.2.1B), or in a minority of cases more than one switch might occur. We therefore computed the probabilities of switching visual percept, of maintaining the same percept, or of switching more than once during the touch period (conditioned to the type of visuo-haptic stimulation: parallel, orthogonal or for a no-touch control period of visual-only stimulation). If haptic stimulation interacts with binocular rivalry dynamics by promoting dominance of the parallel visual stimulus, we would expect the probability of maintaining the same visual percept for the touch period to be higher for parallel visuo-haptic stimulation, or the probability of switching to be higher for orthogonal visuo-haptic stimulation (or both, as in our previous study).

We found that haptic stimulation promoted dominance of the parallel visual percept both by increasing its dominance and by curtailing its suppression (replicating the results obtained in the previous study). When the visual and haptic stimuli were parallel, the probability of *maintaining* the same visual percept during the whole touch period increased by 30% relative to orthogonal visuo-haptic stimulation, and by 21% relative to no-touch control periods. Conversely, when the visual and haptic stimuli were orthogonal, the probability of *switching* visual percept increased by 37% relative to parallel visuo-haptic stimulation and by 19% compared to no-touch periods (Figure 1C, statistics are reported in the figure caption). These results demonstrate that touch specifically interacts with vision during binocular rivalry both by maintaining congruency between the visual and haptic stimuli when the haptic stimulus is parallel to the dominant visual stimulus (retarding rivalry alternations to the orthogonal stimulus in the other eye) and by re-establishing dominance of congruent visual stimulus when it is rendered invisible by binocular rivalry suppression (boosting the suppressed visual stimulus and reverting it to consciousness).

To examine the time-course of the influence of haptic stimulation on the dynamics of binocular rivalry, we computed the instantaneous probability of perceiving the visual grating parallel to the haptic stimulus as a function of time from the onset of a touch period (collapsing parallel and orthogonal visuo-haptic stimulation). If the two rival stimuli are equally likely to be perceived, the probability trace oscillates around chance level. We found that 1 second after the onset of touch the probability trace is significantly biased towards the visual percept parallel to the haptic stimulus (Figure 2.2.2.1D). The effect peaks at 2.35 seconds and slowly decays to chance level at around 4 seconds after the onset of haptic stimulation (1.4 seconds after its offset).

The results presented thus far were for haptic gratings that were either parallel or orthogonal to the dominant visual percept and show a significant effect of touch on vision. Is the effect of touch on vision more finely tuned for orientation? Figure 2 plots the probabilities for maintaining visual percept (left-hand panel) and for switching visual percept (right-hand panel) when the haptic stimulus was mismatched in orientation relative to the visual stimuli by ±7.5°, ±15° or ±30°. Unlike the results for a 0° orientation difference reported above, the data in Figure 2 show clearly that neither the probability for maintaining (Figure2.2.2.2A) nor the probability for switching (Figure 2.2.2.2B) differed from the no-touch control periods when there was a relative orientation difference between the visual and haptic stimuli (statistics reported in the figure caption). While both probabilities peak when visual and haptic stimuli are perfectly matched in orientation (0° difference), the effects of touch at ±7.5°, ±15° and ±30° were not significant for either switching or maintaining. This demonstrates that the interaction between vision and touch during binocular rivalry is strictly orientation tuned.

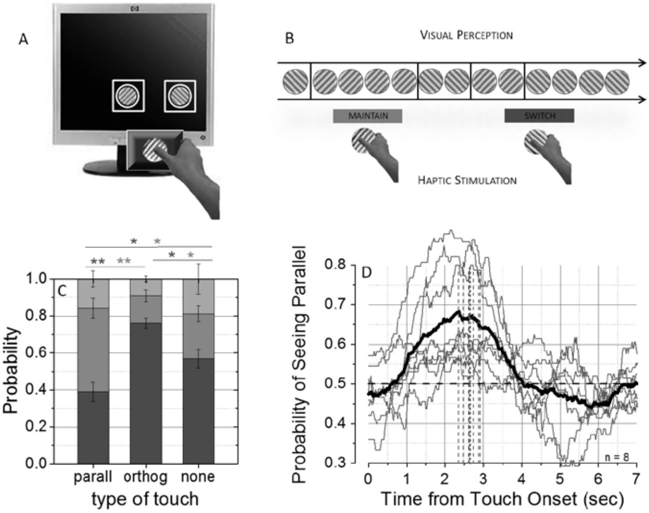


Figure 2.2.2.1. Experimental design and results for matched visuo-haptic orientations.
Panel A shows a diagram of the experimental setup: orthogonal gratings (±45°) were presented separately to the eyes through a mirror stereoscope. During binocular rivalry, at random intervals, observers were asked to explore the haptic stimulus with the right thumb. Panel B shows a diagram of the experimental paradigm that was identical to that of our first study. The probability of switching, maintaining or switching more than once conditioned to the type of visuohaptic stimulation (parallel, orthogonal or no-touch) is plotted in Panel C. When visuohaptic stimulation was orthogonal, the probability of switching (dark grey bars) significantly increased compared both to parallel stimulation (+37%) and no touch periods (+19%). Conversely, the probability of maintaining (light grey bars) significantly increased for parallel visuohaptic stimulation, both compared to orthogonal stimulation (+30%) and to no-touch periods (paired samples t-test, two tailed, α = 0.05, N=8, **p≤0.01, *p≤0.05). The time-course of the effect of touch on binocular rivalry is reported in Panel D, where the average instantaneous probability of perceiving the visual stimulus parallel to the haptic orientation (black line) is plotted as a function of time elapsed from the onset of touch (the grey thin lines represents individual observers traces). The probability trace is significantly biased in favour of the haptic orientation 1.05 seconds after the onset of touch (t-test, two tailed, α = 0.05, N=8), the probability peaks 2.35 seconds after the onset of touch and slowly decays to chance level after the offset of touch (the thick red line represents the average touch duration, while the thin lines the individual observers' ones).

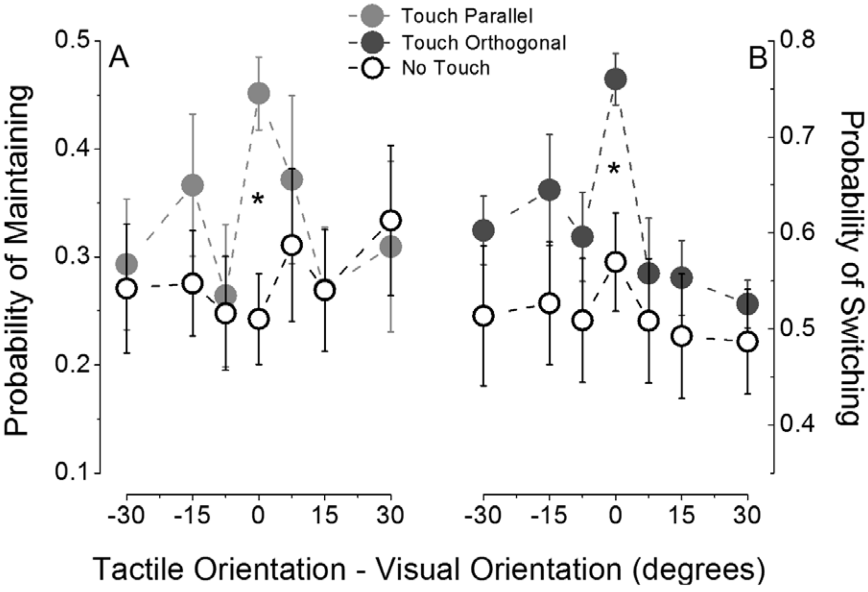
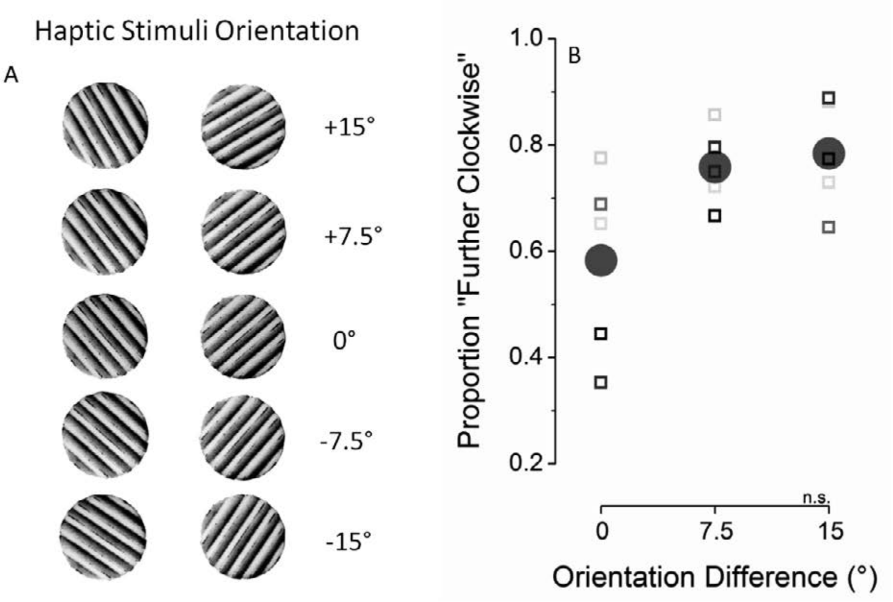


Figure 2.2.2.2. Orientation tuning of the effect of touch on binocular rivalry.
The probability of maintaining the same visual stimulus during the whole touch period when visuo-haptic stimulation is parallel (Panel A, light grey symbols) and the probability of switching perception when visuo-haptic stimulation is orthogonal (Panel B, dark grey symbols), compared to no-touch periods (open symbols) are plotted as a function of the mismatch in orientation between the visual and the haptic gratings (defined as haptic orientation – visual orientation). Both probabilities significantly differ from no-touch periods only when visual and haptic stimuli are perfectly matched in orientation (paired t-test, two-tailed, df=7, p≤0.05).

In the orientation discrimination experiment, similar to the main experiment, the visual stimuli were oriented at ±45° and observers were asked at approximately regular intervals to explore the haptic stimulus with their right thumb. The orientation of the haptic grating was randomly alternated each touch period and could be either clockwise (+45° relative to vertical) with an additional random offset of 0°, ±7.5° or ±15°, or counterclockwise (-45° relative to vertical) with an additional random offset of 0°, ±7.5° or ±15°. A diagram of the haptic orientation pairs is shown in Figure 2.2.2.3A. The visual stimuli alternated in simulated rivalry, as described above, and the observer's task was to track the visual alternations by continuous keypress, thereby matching the conditions of the discrimination experiment and the original rivalry experiment as closely as possible. Only touch periods in which observers accurately reported the visual orientation were considered for analysis. While tracking their visual perception, observers also judged during touch periods whether the haptic stimulus was tilted clockwise or counterclockwise relative to the visual stimulus (using a two-pedal floor switch). Because the visual stimulus was alternating, in some touch periods the haptic grating was aligned (or nearly so) with the visual grating (0°, ±7.5° or ±15°) while in other touch periods is was about 90° away (90° + 0°, ±7.5° or ±15°), as in the orthogonal visuo-haptic presentation condition during the main binocular rivalry experiment. In either case, the response required was the same (the haptic grating was either clockwise or counterclockwise of the visual grating).

Figure 2.2.2.3. Cross-modal orientation discrimination experiment: haptic stimuli and results.



Panel A shows the different haptic orientations used during the experiments. In the main experiment pairs of orthogonal haptic orientations were tested within every experimental block. In the cross-modal orientation discrimination experiment, clockwise and counterclockwise haptic orientations were tested in separate blocks, observers were required to judge to haptic orientation compared to the visual orientation during simulated binocular rivalry. Participants were forced to report whether the haptic stimulus was oriented “further clockwise” or “further counterclockwise” compared to the congruent visual stimulus (either +45° or -45° relative to vertical). Panel B reports the proportion of “further clockwise responses” plotted as a function of the mismatch in orientation between the haptic and the visual stimuli. The small coloured symbols represent individual observers’ performances (every colour representing a different observer), the big transparent grey dots represent the average performance. Even though a trend of improving performance with increasing visuo-haptic orientation difference is present, observers’ performance did not significantly differ from the average performance for visuo-haptic stimuli matched in orientation neither for the 7.5 degrees difference (one sample t-test, df=4, t=2.405, p=0.074), nor for the 15 degrees difference for the 7.5 degrees difference (one sample t-test, df=4, t=1.95, p=0.123), meaning that they were not able to discriminate the difference in orientation between visual and haptic stimuli within 15° difference. A (non significant) bias towards the “further clockwise” response was also observed when visuo-haptic stimuli were matched in orientation.

The results of the visuo-haptic orientation discrimination experiment are reported in Figure 2.2.2.3B which plots the proportion of “further clockwise” responses as a function of angular difference. Threshold performance in this orientation discrimination task is 0.50 correct, however for a visual-haptic orientation difference of 0°, there was a bias to respond "clockwise". That is observers judged the haptic stimulus matching the visual stimulus orientation as being oriented "further clockwise" ~60% of the time. For this reason, we compared the +7.5° and +15° conditions shown in Figure 3B with average performance in the 0° condition, rather than the unbiased threshold of 50%. Performance for orientation differences of +7.5° and +15° did not significantly exceed performance in the 0° condition, implying that observers were not able to discriminate the orientation difference between visual and haptic stimuli even when they differed by 15°. Importantly, discrimination performance in the "further counterclockwise" conditions (-7.5° and -15°), although not shown, did not differ significantly from the "further clockwise" conditions. These results indicate that participants were not aware of the visuo-haptic mismatch in orientation during the main experiment. That is, even though the effect of touch on rivalry in the main experiment was confined to perfectly aligned visual and haptic stimuli (0° orientation difference), these discrimination data show that observers were not aware of the difference between 0° and 7.5°, or between or 0° and 15°. The lack of awareness of the visuo-haptic orientation difference therefore suggests that the strict orientation tuning found in the main experiment is not likely to be attributable to a categorical decision.

2.2.2.3. Discussion

We have shown that exploring a haptic grating while experiencing binocular rivalry between orthogonally oriented visual gratings can substantially influence the alternation dynamics of binocular rivalry. Touching a grating that is congruent with the visual grating being perceived increases the likelihood that it will remain dominant. Conversely, touching a grating that is orthogonal to the visually perceived grating increases the probability that perception will switch to the suppressed grating and therefore align the visual and haptic percepts (Figure 1D). Because the influence of the haptic grating acts not only on the perceptually dominant visual grating but also on the grating rendered invisible by binocular rivalry suppression (in contrast to attentional effects on rivalry, which generally influence only the dominant grating, Chong, Tadin, & Blake, 2005; Paffen & Alais, 2012), these results show that the influence of touch on vision during binocular rivalry occurs outside of visual awareness and is therefore an automatic and compulsory interaction.

One interesting aspect of the data is the relatively slow time course of the effect of touch in promoting dominance of the parallel visual stimulus. When we computed the dynamics of the touch effect we found it takes at least 1 second to significantly bias rivalry and takes more than 2 seconds to peak after touch onset (Figure 1C). The slow time course is probably due to the role of adaptation and reciprocal inhibition in determining binocular rivalry dynamics. As was recently shown (Alais, Cass, O'Shea, & Blake, 2010), sensitivity to the two competing visual stimuli slowly changes during a single rivalry phase: initially sensitivity to the dominant stimulus is high and sensitivity to the suppressed stimulus is low. During a rivalry period, the sensitivity difference reduces due to adaptation of the dominant response and a corresponding release from inhibition of the suppressed response, reaching a near-zero difference just prior to a perceptual switch. Clearly, when the sensitivities to the competing stimuli are very similar (near the end of a rivalry period), the potential for haptic input to bias visual competition would be greater. In our paradigm the touch stimulation was delivered at random moments relative to the rivalry process (near the middle of a rivalry phase, on average) and so we would expect the touch effect to increase over time as the current rivalry period extends and the relative strength of the visual stimuli converges. The time needed for touch to reach the peak effect therefore reflects the time-course of visual adaptation, and is not indicative of the time taken for haptic signals to feedback into early visual areas.

One of the striking findings in this study is that the influence of touch on vision in binocular rivalry is orientation tuned, and very narrowly so (Figure 2). Indeed, our data show that the interaction requires matched visuo-haptic orientations, as a mismatch of 7.5° between visual and haptic orientations was sufficient to annul the effect of touch on binocular rivalry. We explored this narrow tuning further in a visuo-haptic orientation discrimination experiment. The results showed that observers were not able to discriminate a 7.5° visuo-haptic orientation difference as being different from a 0° orientation difference (Figure 3). Nonetheless, although they were perceptually indistinguishable in orientation, our orientation tuning experiment established clearly that 7.5° was ineffective at biasing rivalry dynamics (Figure 2). This pattern of orientation tuning shows a selectivity for orientation that is finer than conscious discrimination, suggesting that the unisensory signals do not need to be individually processed before being integrated. This is contrary to what would be expected in an optimal integration framework in which integration is thought not to be mandatory when integrating between the senses and which is thought to occur at a higher-level of processing after unisensory encoding (Hillis, Ernst, Banks, & Landy, 2002).

Fine orientation tuning is a characteristic of both early visual cortex (Hubel, Wiesel, & Stryker, 1977) and early somatosensory cortex (see Hsiao et al (Hsiao, Lane, & Fitzgerald, 2002) for a review) and links between visual and somatosensory systems has indeed been demonstrated (Fitzgerald, Lane, Thakur, & Hsiao, 2006; Zangaladze, Epstein, Grafton, & Sathian, 1999). In primary visual cortex, single-unit recordings show that cells typically exhibit a sharp orientation tuning with a bandwidth of approximately 15°, a bandwidth consistent with behavioural studies of orientation perception (Bradley, Skottun, Ohzawa, Sclar, & Freeman, 1987). Narrow orientation tuning of V1 cells has been reported in neurophysiological studies (Movshon & Blakemore, 1973; Phillips & Wilson, 1984). Given that the interaction between visual and haptic signals during binocular rivalry is tightly tuned for orientation, we conclude it is likely mediated by early visual neurons. This conclusion reinforces the hypothesis first advanced by Lunghi et al (Lunghi, Binda, & Morrone, 2010) that neural signals for touch and vision interact at the earliest stages of visual processing, probably V1. These authors based their conclusion on the fact that the visuo-haptic interaction they observed in binocular rivalry was tightly tuned for spatial frequency. Our finding of a tight orientation-tuned effect of touch on vision perfectly complements their finding and adds converging evidence for an early visuo-haptic interaction.

The orientation tuning of the visuo-haptic interaction that we observed is actually narrower than that shown by visual neurons. One potential explanation of this we considered was that it was a case of 'categorical perception', a kind of non-linear perceptual response that can change abruptly around a boundary. Examples of categorical visual perception have been found in face perception (Viviani, Binda, & Borsato, 2007), familiar objects perception (Newell & Bulthoff, 2002) and colour perception (Raskin, Maital, & Bornstein, 1983). To explain the orientation tuning of our effect, a categorical perceptual response could be envisaged which is thresholded to occur only when the visual and haptic gratings are iso-oriented and otherwise produces a null response. We specifically tested this hypothesis in our discrimination experiment by testing whether subjects were aware of small differences between visual and haptic orientation. The categorical perception hypothesis predicts they would be aware of the small differences because of its all-or-none response around 0°. The fact that participants could not consciously discriminate the visuo-haptic mismatch in orientation within 15° difference (Figure 3) rules out the categorical perception hypothesis and instead suggests that the angular differences tested (0°, ±7.5°, ±15°) fell within a single orientation bandwidth and were therefore difficult to discriminate. The discrimination data also rule out a 'response bias' account of the peak interaction at 0° because any tendency to respond in a biased way to 0° would be evident for all orientations since they are perceptually indistinguishable.

Another possible explanation of the narrow visuo-haptic orientation tuning is that it occurs as a result of optimal multisensory integration according to the maximum likelihood estimation (MLE) model. In the MLE model (Ernst & Banks, 2002), multisensory signals are first encoded by unisensory processes and these estimates are then combined in a weighted linear sum. The weight for each sensory component is proportional to that component's reliability, given by the inverse of its variance. The model predicts that the combined estimate should have a lower variance than the unisensory estimates because of the following formula: $\sigma^2_{VH} = (\sigma^2_V {*} \sigma^2_H)/(\sigma^2_V+\sigma^2_H)$, where σ^2_v is the variance of the visual estimate and σ^2_H the variance of the haptic estimate. The maximum improvement (lowering) in variance is by a factor of 2, which occurs when $\sigma^2_H = \sigma^2_V$ (Alais & Burr, 2004; Ernst & Banks, 2002; Ernst & Bulthoff, 2004). More relevant to orientation bandwidths, this means the visuo-haptic standard deviation (σ_{VH}) is reduced by a factor of $\sqrt{2}$. Could the MLE model therefore explain why the orientation tuning for the visuo-haptic interaction is narrower than is typically found in vision or in haptic perception? We think this is unlikely for several reasons. First, visual and haptic orientation tunings are not equal: the haptic tuning is broader than the visual one (Fitzgerald, Lane, Thakur, & Hsiao, 2006; Hsiao, Lane, & Fitzgerald, 2002) and hence the maximum reduction in σ_{VH} of $\sqrt{2}$ is not expected. Second, even making the assumption of equal bandwidths for visual and haptic orientation perception (which may be warranted because rivalry suppression has been shown to broaden visual orientation tuning, Ling & Blake, 2009), the sharp visuo-haptic orientation tuning we observed is much more than a factor of $\sqrt{2}$ narrower than the unisensory tunings and so is incompatible with the MLE model.

A possible explanation for the sharp orientation tuning that we found would be to consider the haptic signal acting as a broadly orientation-tuned contrast pedestal. Cross-sensory pedestal effects between vision and touch have been recently found and are thought to reflect an early interaction between the two modalities. Arabzadeh et al (Arabzadeh, Clifford, & Harris, 2008) demonstrated that a visual flash presented near the fingers during a simple haptic discrimination task was able to reproduce the classical 'dipper effect' and improve near-threshold stimulus discriminability, as if the haptic signal had a direct input into the visual mechanism and provided the equivalent of a contrast pedestal. Similarly, in a speed discrimination task, Gori et al (Gori, Mazzilli, Sandini, & Burr, 2011) showed cross-sensory facilitation between vision and touch that resulted in a two-fold improvement of discrimination thresholds that was specific for matched visuo-haptic motion direction. Together, these two findings suggest that the haptic signal in our experiment, which is likely to be broadly tuned after being remapped into visual coordinates and fed back to early visual cortex, effectively provided a contrast pedestal for vision, thereby improving visual orientation discrimination and producing a very sharp tuning.

Overall, our results add further converging evidence in support of the view that multisensory processing is present even in primary sensory cortices. Support for this view comes from a number of neurophysiological and anatomical studies showing unisensory inputs into other unisensory areas (for review see Driver & Noesselt, 2008; Ghazanfar & Schroeder, 2006), as well as from sensory deprivation studies (reviewed in Alais et al (Alais, Newell, & Mamassian, 2010)) showing rapid recruitment of primary visual cortex for haptic processing observed in blind patients (Goyal, Hansen, & Blakemore, 2006; Sadato et al., 1996). Indeed, even temporary loss of sight (e.g., 5 days) is sufficient to induce superior haptic performance in blindfolded individuals (Kauffman, Theoret, & Pascual-Leone, 2002; Merabet et al., 2008). Such rapid recruitment suggests somatosensory connections are not created *ex novo* after sensory deprivation but are already present in primary visual cortex in normal functioning and can be strengthened if needed (Pascual-Leone, Amedi, Fregni, & Merabet, 2005). In normal subject, these connections are likely to be weak compared to vision and easily masked by strong and reliable visual input. We propose that the inherent signal ambiguity in binocular rivalry, in which two equally salient visual stimuli engage in a struggle for perceptual dominance, allows these relatively weak somatosensory inputs to exert a significant influence on early visual processing.

2.2.3. Spatial proximity is crucial, active exploration is not.

In the previous studies we used binocular rivalry to investigate cross-modal interactions between haptic and visual signals. We showed that a haptic signal can rescue the visual stimulus congruent in orientation from binocular rivalry suppression, and that the interaction between visual and tactile signals during binocular rivalry is strictly tuned for matched visuo-haptic spatial frequencies and orientations. From these sets of evidence, we inferred that the haptic signal boosts the suppressed visual signal at the very early stages of visual processing, probably V1 or V2. This hypothesis is consistent with the existence of projections from the polysensory areas of the temporal lobe to V1 in monkeys (Falchier, Clavagnier, Barone, & Kennedy, 2002), with the evidence that the primary visual cortex of rats responds to tactile discrimination of novel objects, and its activity correlates with tactile discrimination performance in an aperture discrimination task (Vasconcelos et al., 2011). Consistently, in normal sighted humans, BOLD studies show that primary visual cortex is activated during exploration of tactile dots (Merabet et al., 2007). V1 is recruited for tactile processing in blind patients (Sadato et al., 1996) and in normal sighted humans after prolonged blindfolding (Merabet et al., 2008). We therefore suggested that visual instability during binocular rivalry can reveal the somatosensory connections to primary visual cortex that are normally masked by the strong visual input.

We performed another set of experiments showing that the interaction between visual and tactile signals during binocular rivalry requires spatial overlap between visual and tactile stimuli, suggesting that already at the level of V1 – the putative site of the interaction – there must be a dynamic alignment between the two sensory spatial maps. In addition, we show that the effect does not require active exploratory action or an attentional allocation of the subject. However, the spatial frequency of the texture of the object must be closely matched.

2.2.3.1. Materials and Methods

Subjects

Ten subjects (three males, average age 28±3.9 years), including one of the authors, participated in the experiment (subject AS took part only in two conditions); all had normal or corrected-to-normal vision, normal stereo acuity (Frisby Stereotest, (Sasieni, 1978), with no strong eye dominance. Subjects gave informed consent. The experiments were carried out along the principles laid down in the declaration of Helsinki, and with approval of the relevant ethics committees.

Apparatus and Stimuli

The experiment took place in a dark and quiet room. Visual stimuli were created in MATLAB using PsychToolbox (Brainard, 1997), and displayed on a 24-inch monitor (Acer LCD GD245HQ), hung 37 cm over an opaque mirror. Observers viewed the reflection of the monitor at a distance of 20 cm from the mirror through anaglyph red-blue goggles (right lens blue, left lens red). Responses were recorded through the computer keyboard. Visual stimuli were two oblique orthogonal red and blue gratings (orientation: ±45°, size: 3°, SF 2 cpd or 3.5 cpd, contrast 30%), surrounded by a white smoothed circle, presented on a black uniform background in central vision. Peak luminance of the red grating was matched with the physical peak luminance of the blue one (2.13 cd/m^2). The edges of the mirror were hidden by a black cloth, minimizing visual references. The tactile stimulus was a sinusoidal grating (size: 3 cm, SF: 2c/cm) created with a 3D printer (Dimension Elite SST, Stratasys, Inc., Eden Prairie, MN). The stimulus was attached to a prop that could be moved 3 cm back and forth under computer control with a linear trajectory at constant speed of 2.5 cm/sec. The motor and the stimulus prop were positioned under the mirror, with the tactile stimulus being at the same distance of the monitor (37 cm from the mirror), so that the visual stimulus was projected exactly on the tactile one. The orientation of the tactile stimulus could be changed by lever. Fig 2.2.3.1F illustrates the set-up.

Task and Procedure

Binocular Rivalry. Each observer participated in five 180-sec experimental sessions x five experimental conditions for a total time of 75 minutes, over different days. The three main tactile conditions were *active exploration*, *passive touch*, *touch away*. Active exploration and passive touch were tested also with non-matched visuo-tactile Spatial Frequencies (Visual SF: 3.5 cpd, Tactile SF: 2 c/cm). The order of the different conditions was randomized for every observer.

After an acoustic signal (beep) the visual binocular rivalry stimuli appeared. Participants reported their visual perception by continuously pressing with the left hand one of two keys (up or down arrows) of the computer keyboard. They were instructed to track color alternation; at each experimental session the orientation of the rival stimuli was swapped between the eyes. As assessed in training binocular rivalry sessions and in debriefing sessions, mixed percepts occurred for very brief periods, only during perceptual transitions, and their frequency remained constant across conditions.

In the *active exploration* condition, during the observing period, at approximately regular intervals, observers were asked by the experimenter (verbal instruction) to explore the tactile stimulus with their right index finger performing a constant translational movement, until the experimenter gave a stop signal (average touch period: 2.5±0.15 sec). At each touch period the orientation of the tactile stimulus was manipulated by the experimenter alternating the clockwise and counterclockwise orientations following preset random generated sequences (the orientation of the stimulus was unpredictable at each touch period). Touch periods timing and stimulus orientation were recorded by the experimenter by holding the proper mouse button.

The *touch away* condition was identical to the *active exploration* except that the tactile stimulus was positioned 30 cm away (on the horizontal axis) from the location corresponding with the visual stimulus (center). At each touch period the observer accomplished a movement with the arm to reach the tactile stimulus (average touch period: 2.6±0.14 sec) and then went back to the resting position (centered on the visual stimulus).

During the *passive touch* condition, the tactile stimulus was drifted 3 cm back and forth at 0.83 Hz. Observers wore insulating headphones to attenuate the sound of the motor, and kept their right index finger stationary on a foam rubber guide. The dynamics of the experiment were the same, except that touch periods were delivered by the experimenter using a lever that elevated the tactile stimulus to touch the finger pad of the participant (average touch period: 2.6±0.15 sec, 2.8±0.14 sec for the mismatched spatial frequency condition).

Tactile Priming. Two tactile priming durations (10 and 3 seconds) were tested in separate blocks comprising 30 consecutive trials. When cued by the acoustic signal (beep), together with the written instruction to “touch” observers started to actively explore the tactile stimulus with the right index finger. After 10 or 3 seconds (depending on the condition), a second beep sounded and the observers raised their finger from the stimulus, and the visual stimuli were displayed (red-blue gratings) for 3 seconds. The temporal delay from the beep signaling the end of touch and the presentation of the visual stimuli was set to 500 ms, but the actual separation between the end of touch and the visual stimulus depended on the RT of the subjects. Using the computer keyboard, observers were asked to report their first percept (red or blue) by appropriate key pressing. A 2 seconds break was interleaved between trials, during which the experimenter changed the orientation of the tactile stimulus following preset random generated sequences. At each trial the orientation of the visual grating was swapped between the eyes.

2.2.3.2. Results

Interaction between visual and tactile signals during Binocular Rivalry

We measured the effect of touch on binocular rivalry for active exploration and passive tactile stimulation conditions in separate blocks. In order to reduce the possibility of response bias, in all conditions observers were asked to track the color of the dominant stimulus (red or blue) and not the orientation (that was randomly associated with one of the two at every experimental block). In the conditions requiring active exploration of the tactile stimulus, observers were asked at random intervals to explore the tactile stimulus with a horizontal movement of the right index finger. In the passive touch conditions the right index finger of the observer was stationary on a prop and tactile stimulation was passively delivered with the tactile patch moving at a constant velocity of 2.5 cm/s. The touch periods were brief (average 2.5s) and interleaved with vision-only stimulation; at each touch period the visual and the tactile stimuli could randomly be parallel or orthogonal to each other.

We first computed the probability of switching, maintaining the same percept or switching more than once for the different conditions of visuo-tactile stimulation: parallel, orthogonal or, as a control condition, for period of visual only stimulation of comparable duration (Fig 2.2.3.1A-E).

In the active-touch condition, when the visual and the tactile stimuli were parallel, the probability of maintaining the same percept for the whole touch period (Fig 2.2.3.1A, orange bars) increased by 32% compared with orthogonal visuo-tactile stimulation and by 20% compared with no-touch periods. When the visual and the tactile stimuli were orthogonal, the probability of switching (Fig 2.2.3.1A, green bars) increased by 37% compared with parallel visuo-tactile stimulation and by 25% compared with no-touch periods. Consistent with our previous studies, active tactile stimulation influenced the dynamics of binocular rivalry, both by prolonging dominance and by curtailing suppression of the visual percept parallel to the tactile stimulus. Interestingly, the same result held for the passive-touch condition (Fig 2.2.3.1B): during parallel visuo-tactile stimulation the probability of maintaining the same percept for the whole touch period increased by 27% compared with orthogonal visuo-tactile stimulation and by 17% compared with no-touch periods; similarly during orthogonal visuo-tactile stimulation the probability of switching increased by 32% compared with parallel visuo-tactile stimulation and by 21% compared with no-touch periods. In the passive condition the tactile signal was purely sensory: voluntary attention to the finger and active action were not involved (the finger was stationary in a resting position with tactile stimulation passively delivered by the experimenter, his/her only task was to report visual perception).

Spatial proximity is known to be crucial for cross-sensory integration (Gepshtein, Burge, Ernst, & Banks, 2005). To test if it is also crucial in modulating the visual rivalry, we repeated the experiment by placing the tactile stimulus 30 cm away from the visual stimulus apparent location; at each touch period observers were trained to reach the tactile stimulus, explore it with the right index finger and, after the stop signal, go back to the resting position aligned with the visual stimulus. We introduced the movement of the arm to re-set proprioception, that is known to drift in the dark (Desmurget, Vindras, Grea, Viviani, & Grafton, 2000). When the visual and the tactile stimulus occupied different locations (touch away condition) tactile stimulation did not influence the dynamics of binocular rivalry: none of the probabilities differs across visuo-tactile conditions (Fig 2.2.3.1C). Touch was ineffective also when the visual and the tactile stimulus were mismatched in spatial frequency at the same location (i.e. spatial frequency of the visual stimulus was 3.5 c/cm, while the tactile spatial frequency was 2 c/cm): maintaining, switching (once or more than once) are equally likely across visuo-tactile conditions both for active exploration of the tactile stimulus (Fig 2.2.3.1D) and passive tactile stimulation (Fig 2.2.3.1E).

A factorial 5x3 repeated measures ANOVA revealed a main effect of the type of tactile stimulation (parallel, orthogonal or none) both for the probability of maintaining the same percept for the whole touch period (F=17.704, p≤0.001) and for the probability of switching once (F=8.639, p≤0.01), but not for the probability of switching more than once (F=0.955, p=0.406). A main effect of experimental condition was found only for the probability of performing one switch during the touch period (F=3.085, p≤0.05). A significant interaction of the two factors (experimental condition x type of touch) was found both for the probability of performing one switch during the touch period (F=23.458, p≤0.001) and for the probability of maintaining the same percept during the whole touch period (F=6.806, p≤0.001), but not for the probability of performing multiple switches s(F=1.975, p=0.065). The probability of maintaining and performing one switch significantly differed for the different type of tactile stimulations only for the active and passive touch conditions, as revealed by a paired two tailed t-test (Fig 2.2.3.1).

We further analyzed the timecourse of the effect of touch on binocular rivalry by computing the instantaneous probability of seeing the visual stimulus parallel to the tactile stimulus as a function of time elapsed from the onset of touch (Fig 2.2.3.2A-E). All touch periods (independently from the type of visuo-tactile stimulation) were aligned at time zero, therefore the probability trace starts at chance level (with some random variability). In the active-touch condition (Fig 2.2.3.2A), the average probability increased over time and reached statistical significance 0.7 s after the onset of touch, peaked at 1.7 s and then slowly decayed over time back to chance 1.5 seconds after the end of tactile stimulation. In the passive-touch condition, the probability trace reached statistical significance 1 s after the onset of touch, peaked at 2.3 s and reverted to chance 1 s after the end of tactile stimulation. The timecourse of the effect was slower than the active touch condition, while the decay of the effect was faster. Consistently with the average probabilities, when the visual and the tactile stimuli were in different locations (Fig 2.2.3.2C) or were mismatched in spatial frequency (Fig 2.2.3.2D-E), the average probability trace was nearly flat and never reached a statistical significant difference from chance level, indicating again that tactile stimulation did not interact with binocular rivalry under these conditions. Taken together these results show that spatial proximity and spatial frequency matching between visual and tactile stimuli are necessary conditions for their interaction during binocular rivalry, while voluntary attention and action enhance the effect of touch on binocular rivalry, but are not necessary to attain the interaction.

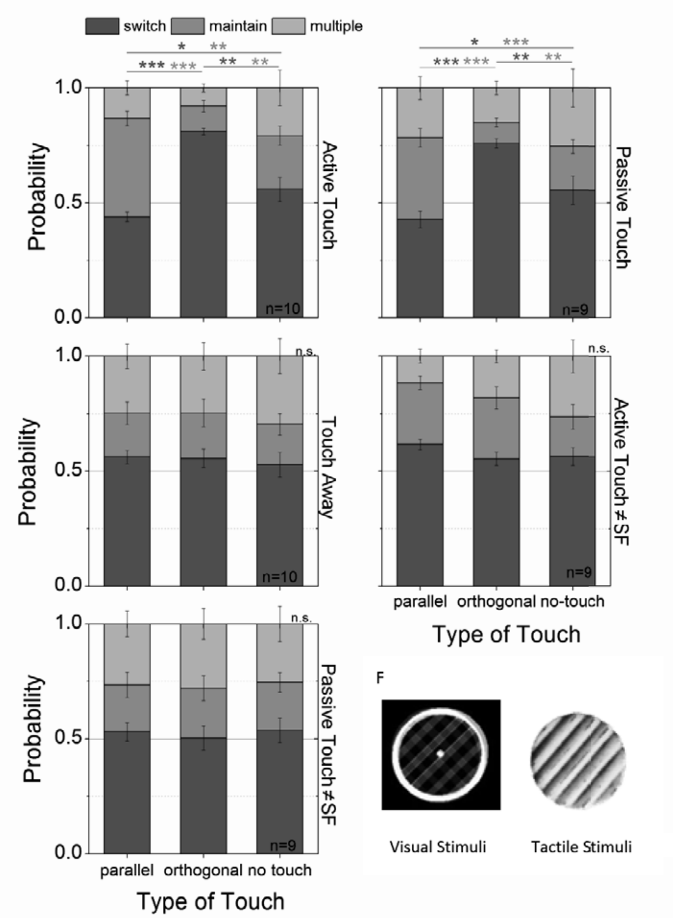


Figure 2.2.3.1. Average Probabilities across Touch Conditions.
The average probabilities of switching visual perception once (dark grey bar), maintaining the same visual percept (light grey bar) or switching more than once during a touch period (gray bar), depending on the type of visuo-tactile stimulation (parallel, orthogonal or no-touch periods of comparable duration), plotted for the different experimental conditions (the error bars represent s.m.e.). Tactile stimulation influenced the dynamics of binocular rivalrly both during Active- and Passive-Touch conditions (Panel A-B): the probability of switching was significantly higher when the visual percept was orthogonal to the tactile stimulus, while the probability of maintaining the same visual percept for the whole touch period was significantly higher for parallel visuo-tactile stimulation (paired t-test, n=10, two tailed, $\alpha = 0.025$, $*=p \leq 0.025$, $**=p\leq 0.01$, $***=p \leq 0.001$). When the visual and the tactile stimuli were in different locations, tactile stimulation had no effect on binocular rivalry (Panel C): none of the probabilities differed across visuo-tactile conditions. Tactile stimulation was also ineffective when the visual and the tactile stimuli were mismatched in Spatial Frequency, both for Active (Panel D) and Passive (Panel E) touch. Panel 1F shows the visual and the tactile stimuli. The visual stimuli were orthogonal red and blue gratings oriented at ±45°, presented separately to the eyes through anaglyph red and blue goggles; the tactile stimulus was an engraved sinusoidal grating matched in Spatial Frequency with the visual stimuli (2c/cm).

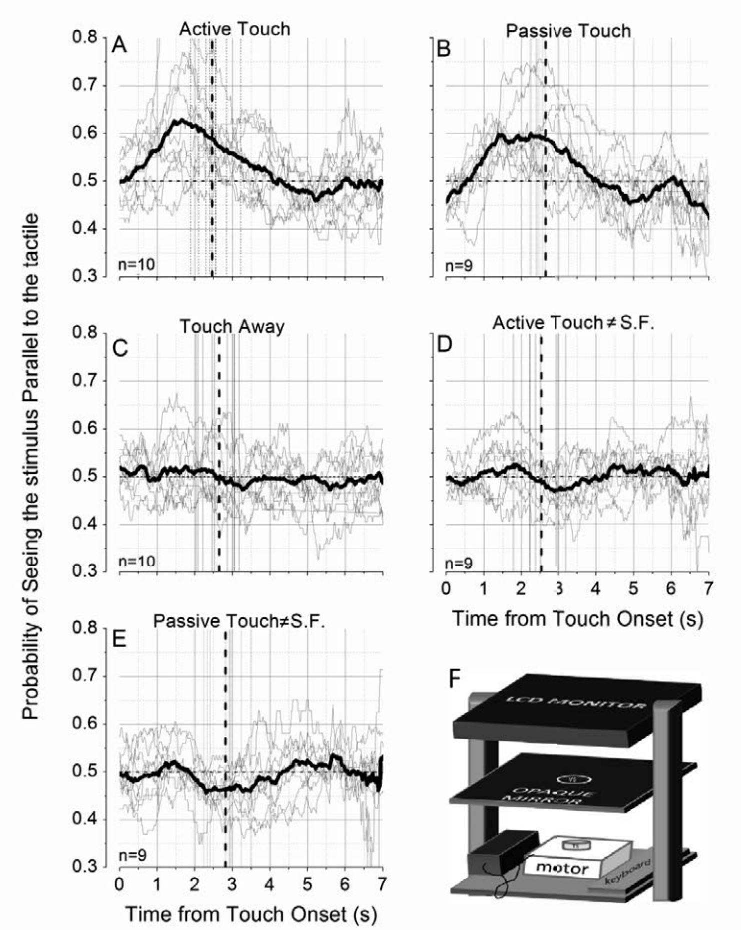


Figure 2.2.3.2. Timecourse of the effect.

The instantaneous probability of perceiving the visual stimulus parallel to the tactile stimulus is plotted as a function of time elapsed from the onset of touch. All touch-periods are aligned at time zero. The gray thin lines are the single subject traces, while the black thick line is the average trace. The vertical dashed line represent the average duration of a touch period. The two visuo-tactile conditions (parallel and orthogonal) are collapsed together. In the Active-Touch condition (Panel A) the probability trace is significantly biased towards the visual stimulus parallel to the tactile stimulus 0.724 s after the onset of touch, peaks at 1.65 s and then slowly decays to chance. In the Passive-Touch condition (Panel B) the probability trace is significantly higher than chance 0.96s after the onset of touch, peaks at 2.31 s and then slowly decays over time. When the visual and the tactile stimuli were in different locations (Panel C), or when the visual and the tactile stimuli were mismatched in Spatial Frequency (Panels D-E), the probability trace was flat and never significantly different from chance (T-test, two tailed, α = 0.025). Panel 2F is a cartoon of the experimental setup: an opaque mirror was placed half way between the monitor and the tactile stimulus (TS), so that the visual stimulus (VS) was projected onto the TS location. Responses were collected through the keyboard. In the Passive-Touch condition, the TS was moved by a motor and tactile stimulation was delivered by the experimenter.

Tactile priming on Onset Rivalry

The survival of the effect during passive tactile stimulation rules out the possibility that voluntary action-related attention plays a critical role in mediating the interaction. We ran another experiment in which one of the two rival images was primed by a tactile cue before the onset of rivalry. Object-based attention is known to drive the first coherent percept of binocular rivalry: if a visual cue is presented before the onset of rivalry, the first dominance phase will tend to be that of the cued stimulus (Chong & Blake, 2006; Hancock & Andrews, 2007; J. F. Mitchell, Stoner, & Reynolds, 2004). We therefore sought for a similar cross-modal effect by having observers explore the tactile stimulus for 10 s the in absence of visual stimulation, as they raised the finger, the visual stimuli were displayed for 4 seconds, and observers had to report their first coherent percept. The average delay between the cue and presentation of the visual stimuli was 500 ms, but the separation from touch was variable according to the promptness of observers in raising their finger when instructed.

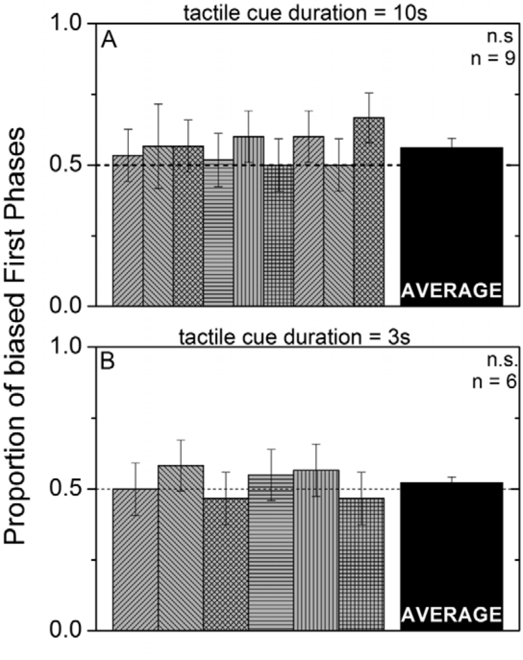


Figure 2.2.3.3. Tactile priming on Onset Rivalry.
The proportion of first coherent percepts parallel to the tactile cue orientation is plotted for two conditions: in the first (Panel 3A) the duration of the tactile cue was 10 seconds, in the second condition (Panel 3B), the duration of the tactile cue was 3 seconds. The tactile cue did not prime the onset of rivalry: on average, the proportion of first dominance phases parallel to the tactile cue did not statistically differ from chance level (T-test, two tailed, α=0.025). The grey bars represent the single subjects' data.

We found that the tactile cue did not bias the onset of rivalry: on average, the first coherent percept of binocular rivalry was at chance level relative to the tactile cue orientation (Fig 2.2.3.3A). In our paradigm 10 seconds of tactile stimulation did not affect the onset of rivalry in any direction, indicating that neither tactile priming or tactile adaptation occurred. We noticed that observers' first dominant percept remained virtually unchanged: the visual stimulus presented to their dominant eye (irrelative of orientation) dominated most of the times and the tactile cue did not affect it. We repeated the experiment shortening the duration of the tactile cue to 3 sec to match the duration of touch periods during binocular rivalry, but nevertheless, tactile stimulation did not prime the onset of rivalry (Fig 2.2.3.3B).

2.2.3.3. Discussion

The results of this study confirm that tactile signals specifically interact with vision during binocular rivalry promoting dominance of the parallel visual stimulus, both by prolonging its dominance and by shortening its suppression. This latter result indicates that the interaction occurs outside of visual awareness, when the visual stimulus parallel to the tactile stimulus is perceptually suppressed during binocular rivalry. The relatively slow timecourse of the effect of touch on the dynamics of binocular rivalry is in fact indicative of the time taken for the suppressed visual image to recover from the profound adaptation caused by binocular rivalry suppression (Alais, Cass, O'Shea, & Blake, 2010). The timing of the effect reflects the interaction of the tactile feedback to the visual areas with an intrinsically slow dynamics driven by adaptation and reciprocal inhibition between the monocular signals.

The most interesting result of the present study is that the effect requires spatial proximity between the visual and the tactile stimulus, suggesting that the mechanisms mediating the effect have access to a *spatiotopic* spatial map that is invariant with the sensor position. The visual and tactile objects have to be matched also in texture, pointing to a functional role of the interaction. In addition, we demonstrate that an unambiguous tactile signal can resolve binocular rivalry even when tactile stimulation is passively delivered, showing that no voluntary or cross-modal attention or action are necessary to mediate the facilitation. In the study by Lunghi et al, the visual and the haptic stimuli did not overlap (the visual stimulus was presented approximately 15 cm above the haptic stimulus location) and this could be considered contradictory to the present results. However in that study, the haptic and visual stimuli were vertically aligned and laid on the same plane, moreover, both the arm and the hand of the observer were stationary for the whole testing block, with only the right thumb exploring the haptic grating. In this condition the subjects had the illusory perception of touching the visual stimulus probably caused by proprioception adaptation. In the current study, when the visual and the tactile stimuli were misaligned, the observer had to actively reach the tactile stimulus performing a voluntary action that reinforced the perception of misalignment between the visual and the tactile stimulus. Interestingly the effect reported in the current study is slightly stronger than in the previous study, reinforcing the fact that spatial alignment is important.

The unconscious, automatic nature of the effect of touch on binocular rivalry differentiates our results from the vast evidence that optimal integration between cross-sensory signals is not mandatory (Hillis, Ernst, Banks, & Landy, 2002), and from previous studies on cross-sensory interactions with ambiguous visual stimuli. Auditory looming signals, when attended, can prolong the dominance phase of the visual stimulus of congruent temporal frequency during binocular rivalry, but do not curtail its suppression (van Ee, van Boxtel, Parker, & Alais, 2009). The same is true for auditory stimuli semantically congruent with one of the visual rivaling stimuli (a bird and a car respectively: Chen, Yeh, & Spence, 2012) and for an auditory stimulus amplitude modulated at a rate matching one of the rival stimuli spatial frequency (Guzman-Martinez, Ortega, Grabowecky, Mossbridge, & Suzuki, 2012b).

Previous studies have shown that touch can help disambiguate visual perception: touching a rotating globe prolongs dominance of the congruent rotation direction in the kinetic depth effect (Blake, Sobel, & James, 2004), kinestethic information can solve the aperture problem when observers actively move a cube aligned with the visual stimulus in one of the two component directions of the visual stimulus (Hu & Knill, 2010) and touch merges with vision to improve slant discrimination (Ernst, Banks, & Bulthoff, 2000). Fusion between visual and tactile signals during these tasks, however, is not mandatory and requires conscious perception of each of the unisensory signals. This evidence is coherent with the view that cross-modal signals are integrated at higher level associative brain areas only after being analyzed by the unisensory cortices. Our results challenge this view and are in line with a new concept that considers the whole brain as essentially multisensory (Ghazanfar & Schroeder, 2006).

Cross-modal attention modulates the activity of early visual cortices (Macaluso, Frith, & Driver, 2000) and could potentially mediate the effect that we observed. We therefore tested whether a cross-modal cue could prime the onset of rivalry. While exogenous attention has a minor effect on sustained binocular rivalry, there is evidence that an object-based attentional cue presented before the onset of rivalry can substantially bias the first coherent percept in favor of the cued stimulus (Chong & Blake, 2006; Hancock & Andrews, 2007; J. F. Mitchell, Stoner, & Reynolds, 2004). Onset rivalry, in fact, is thought to have different properties from “late” rivalry: it is quite stable and is susceptible to different biases (Stanley, Forte, Cavanagh, & Carter, 2012). The intermittent presentation of the rivalry stimuli “stabilized” binocular rivalry: an effect first described by (Leopold, Wilke, Maier, & Logothetis, 2002) that has been attributed to perceptual memory for ambiguous figures. When primed by touch the observers of the present study reported the same percept over several trials and touch could not disrupt this stabilization. The ineffectiveness of a tactile cue to prime the onset of rivalry suggests that simultaneous presentation of visual and tactile stimuli is a crucial factor for the interaction to occur, and rules out the possibility that the interaction between vision and touch during binocular rivalry could be entirely explained by activating attentive mechanisms with cross-modal cues. This control additionally rules out the possibility of response bias.

It has been demonstrated that voluntary action interferes with a visual signal suppressed by binocular rivalry (Maruya, Yang, & Blake, 2007), the persistence of the effect in the passive touch condition, therefore indicates that the nature of the visuo-tactile interaction is exclusively sensory. Importantly, that the effect of touch on rivalry depends on congruency of visuo-tactile spatial frequency for passive tactile stimulation further confirms that the somatosensory signal alone is sufficient to boost the suppressed visual signal at the very first stages of visual analysis: only neurons of the primary visual cortex in fact show spatial frequency tuning as narrow as less than one octave (Maffei & Fiorentini, 1973), necessary to explain the selectivity of our effect. V1 therefore seems the prime candidate neural locus for the visuo-tactile interaction that we report. The finding that spatial proximity is necessary to fuse the visual and the tactile signals extends the specificity of the interaction: the visual and the tactile signals must be perceived as arising from the same object to be integrated. However, this also poses a problem. V1 neurons code visual space in retinotopic coordinates, while tactile information is initially coded in somatotopic space: only later at parietal levels there is evidence of mapping in visual retinotopic space (Andersen, Essick, & Siegel, 1985). To explain both the spatial frequency selectivity and the spatial alignment of the two sensory maps we have to hypothesize that the interaction take place in V1, but it is mediated by a tactile signal represented in visual retinal coordinates. There is no evidence of direct projections from S1 to V1, but there is evidence of projections from STP (Falchier, Clavagnier, Barone, & Kennedy, 2002) where somatosensory information may be mapped in retinotopic coordinates (Andersen, Essick, & Siegel, 1985). These projections back to V1 may mediate the effect observed here.

Taken together, the results presented here suggest that the interaction between visual and tactile signals during binocular rivalry takes place at the very early stages of visual processing, probably V1. We propose that the somatosensory projections to the primary visual cortex, normally concealed by the strong and unambiguous visual signal are revealed by the temporary blindness caused by binocular rivalry suppression, and are shown in this study to be “retinotopically” coded. These results bring new evidence in favor of a novel role of primary sensory cortices, which have been thought to process only unisensory information, as well as highlighting the debate about neural plasticity following sensory loss.

2.2.4. Summary and Conclusions

We have demonstrated that touch can disambiguate visual perception during binocular rivalry favouring dominance of the congruent visual stimulus both by prolonging its dominance duration and by shortening its suppression. That the tactile signal can rescue the congruent visual signal from binocular rivalry suppression reverting it to consciousness indicates that the interaction between vision and touch during binocular rivalry is compulsory, for it occurs outside of visual awareness. By varying the spatial frequency and orientation of the tactile stimuli we have also shown that the interaction between vision and touch during rivalry is specific, with a very tight tuning for orientation and spatial frequency: the visual and the tactile stimulus need to be perfectly matched both in spatial frequency and in orientation in order to observe the interaction. We have further demonstrated that voluntary attention and action are not necessary conditions for the interaction to occur: passive tactile stimulation is as effective as active haptic stimulation in biasing binocular rivalry. We have instead found that spatial and temporal alignment are crucial factors for the interaction, for placing the haptic stimulus away from the visual stimulus location or delivering tactile stimulation before the onset of visual stimulation annulled the effect of touch on the dynamics of binocular rivalry.

Taken together, the results listed above strongly point to an early interaction between visual and tactile signals during binocular rivalry:

- binocular rivalry suppression occurs early in the visual system, neural activity associated with the suppressed image is not traceable outside V1 or V2. In order to boost the suppressed visual signal, the tactile signal must reach these early visual cortices;
- touch interacts with vision outside of visual awareness, indicating that the interaction can occur before processing of unisensory information;
- neurons showing a tuning for orientation and spatial frequency as narrow as that we found for the interaction are typically found in primary visual cortex;
- spatial and temporal alignment are benchmarks of early cross-modal integration.

We propose that the intrinsic ambiguity of binocular rivalry and the temporary blindness provoked by binocular rivalry suppression are able to reveal the somatosensory connections with early visual cortices, connections that are normally concealed by the strong and reliable visual input. Our results expand the evidence in favour of the involvement of early sensory cortices in multisensory processing, providing psychophysical evidence in favour of an early interaction between vision and touch. In conclusion, our findings support the view that the recruitment of primary visual cortex for tactile processing observed following loss of vision occurs by reinforcing pre-existing connections, rather than by creating them ex-novo.

Chapter 3
Plasticity of adult human visual cortex revealed by binocular rivalry.

3.1. Introduction

Neuroplasticity refers to the capability of the nervous system to be modified by experience. The term *plastic* in fact derives from the Greek word plastòs that means molded. Such experience-induced neural changes may be driven by environmental pressure, functional significance, behavioural relevance and neural activity and can occur through structural or functional alteration both at the macroscopic (i.e. neural connections) and microscopic (i.e. synapses) levels. Neuroplasticity is maximum early in life and is crucial for the development of the organism, for it ensures adaptability to a continuously changing external environment providing an evolutionary advantage for the organism. Besides being an adaptive phenomenon, sometimes neuroplasticity can be "negative", or maladaptive, with experience-driven modifications resulting in pathologies. During adulthood, neuroplasticity is thought to be reduced, especially for low level sensory processing, but it is preserved for higher level properties, for plasticity is the process underpinning learning and memory. Because of its leading role in diverse neural processes, neuroplasticity is thought to be an intrinsic property of the nervous system (Pascual-Leone, Amedi, Fregni, & Merabet, 2005).

In the next paragraphs, we will focus on plasticity of the visual system, reviewing experimental evidence regarding the plastic potential of early visual cortex both during development and adulthood.

3.1.1. Juvenile plasticity of the visual system: the critical period.

The developing mammalian visual system is extremely plastic: early in life, within a particular temporal window called *critical period,* the visual cortex is literarily shaped by experience, for it is immature at birth. After the closure of the critical period, visual plasticity is thought to be severely reduced or even absent, visual cortex being hard-wired during adulthood. Critical periods have been found in all species for different sensory modalities and within a sensory modality for different functions (Berardi, Pizzorusso, & Maffei, 2000). The duration of the critical period varies across species and depends on the feature tested. Since the critical period is a well defined part of the animal life during which neural connections are shaped by experience, its duration is related to the animal lifespan: the longer the lifespan,

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the longer the critical period. While the extraordinary plasticity of the sensory brain is crucial during development, allowing the organism to adapt to the external world escaping the limitations of its gene pool, an excessive duration of the sensitive period would expose the organism to the possibility of maladaptive neural modifications driven by an abnormal visual input. Figure 3.1.1. shows the correlation between the duration of the critical period for ocular dominance (one of the most studied features of the visual cortex that we will detail in the next paragraphs) and the lifespan of different mammal species: mouse (Huang et al., 1999), rat (Fagiolini, Pizzorusso, Berardi, Domenici, & Maffei, 1994), ferret (Issa, Trachtenberg, Chapman, Zahs, & Stryker, 1999), cat (Olson & Freeman, 1980), monkey (Harwerth, Smith, Duncan, Crawford, & von Noorden, 1986) and human (Banks, Aslin, & Letson, 1975). Finally, a correlation also exists between critical period duration and brain complexity (and related brain weight): the more complex the brain, the longer the critical period.

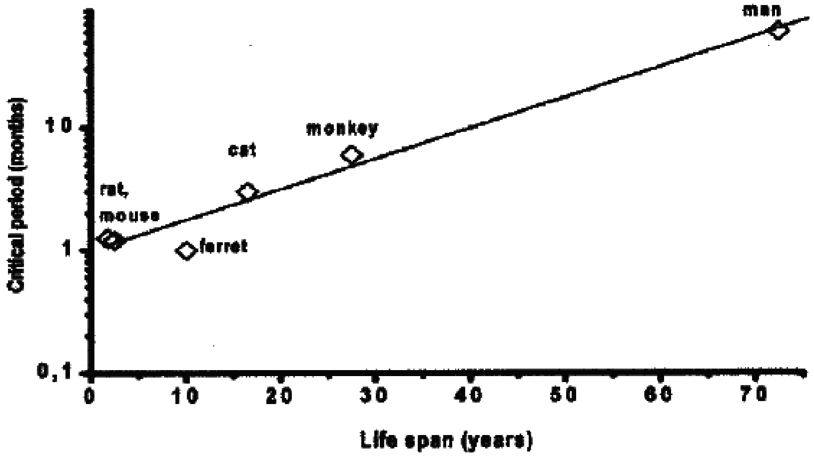

Figure 3.1.1. Ocular Dominance critical period duration and mammal lifespan. Adapted from (Berardi, Pizzorusso, & Maffei, 2000).
The duration of the critical period for ocular dominance has been studied in different mammal species: mouse, rat, ferret, cat, monkey and human. A linear correlation (r=0.98, SD=0.14,p≤0.001) exists between the duration of the critical period and the animal lifespan.

3.1.1.1. Ocular Dominance plasticity during the critical period.

In the young animal, cortical areas are not yet fully specialized for a particular task. Neuroplasticity is the mechanism through which cortical differentiation is refined during the first period of life, tuning cortical activity according to the environmental pressures. The initial sensitive period during which neural connections are shaped by experience is a protection for the young animal, for brain injury can be compensated by other brain areas taking charge of the damaged functionality (Stiles, 2000). On the other hand, as anticipated in the previous paragraph, if for some reason the early experience is inadequate, plasticity will mold brain structure to the abnormal input, causing permanent deficit to the developing organism. One of the most studied cases of this maladaptive form of plasticity is the development of ocular dominance columns and binocularity in the primary visual cortex, that can be severely damaged by inadequate visual input, resulting in amblyopia if vision in one eye is impaired during development.

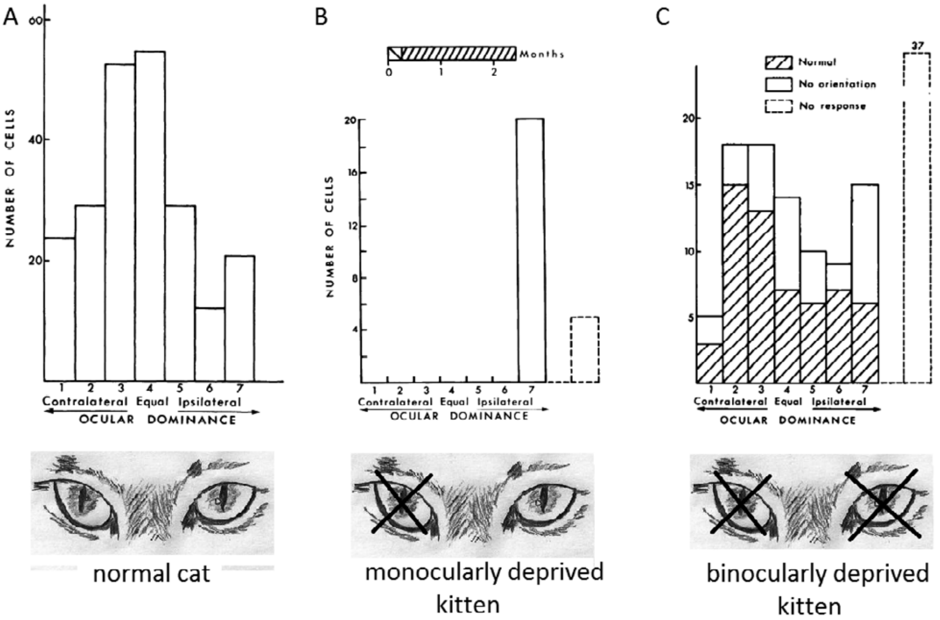

Figure 3.1.2. Effect of monocular deprivation on ocular dominance. Adapted from (Wiesel & Hubel, 1965a)
(A) Organization of ocular dominance in the normal cat, neurons in primary visual cortex are classified according to their monocular preference. Group 1 cells respond only to the contralateral eye, while group 7 cells respond only to the ipsilateral eye. Group 4 neurons respond equally to both eyes, while group 5 and 6 respond to both eyes, but more to the ipsilateral eye and group 2 and 3 respond to both eyes, but more to the contralateral eye. Adapted from (Hubel & Wiesel, 1962) (B) Following monocular deprivation during the critical period, all cortical cells respond to the open eye, while responses to the deprived eye are abolished, and as a consequence, none of the neurons shows binocular responses. Adapted from (Wiesel & Hubel, 1963b) (C) Following binocular deprivation during the critical period, ocular dominance organization of primary visual cortex is almost entirely preserved, showing that competition between monocular inputs is critical for cortical organization.

In the 1960s, the Nobel Prize's David Hubel and Torsten Wiesel studied the development and plasticity of ocular dominance columns in the primary visual cortex of the cat (Hubel & Wiesel, 1962, , 1963, , 1964; Wiesel & Hubel, 1963a, , 1963b, , 1965b). In their pioneering work, Hubel and Wiesel demonstrated how even a short epoch of monocular deprivation during the critical period caused a rearrangement of thalamo-cortical connections in the kitten brain, shifting ocular dominance in favour of the open eye. In the normal primary visual cortex, the majority (4/5) of neurons are binocular, that is they respond to inputs presented to both eyes, while only 1/5 of neuron shows monocular responses. Binocular neurons can be in turn differentiated according to their monocular preference, even though they respond to binocular inputs, in fact, some binocular neurons show a preference for one or the other eye (Hubel & Wiesel, 1962). Hubel and Wiesel (1962) classified neurons in the primary visual cortex of the adult cat according to their monocular preference, individuating seven different classes of neurons, where neurons of group 1 are completely driven by the contralateral eye and neurons of group 7 are totally driven by the ipsilateral eye (Figure 3.1.2.A). Neurons falling in the intermediate groups respond to input from both eyes, but show a preference for either the contralateral or the ipsilateral eye, with only neurons of group 4 responding equally to stimuli presented to the two eyes (Hubel & Wiesel, 1962). In a subsequent study, ocular dominance organization of young kittens has been showed to be very similar to that of the adult (Hubel & Wiesel, 1963).

Monocular deprivation has been classically used as a probe for ocular dominance plasticity: if, during the critical period, one eye is deprived of vision either by lid suture or by the application of an opaque contact lens, the deprived eye loses the ability of driving cortical activity, and all cortical neurons respond to the normal eye, becoming therefore monocular (Figure 3.1.2.B). The normal eye takes over the connections of the deprived eye, which results in a shrinkage of ocular dominance columns of the deprived eye and a relative enlargement of those of the open eye. As a result, the kitten becomes amblyopic, with defective vision (loss of visual acuity) in the eye that had been deprived as well as a loss of binocular vision, with consequent behavioural disadvantages (Wiesel & Hubel, 1963a; 1963b). The deafferentation of primary visual cortex observed following monocular deprivation is due to the weakening, and eventually deletion, of thalamo-cortical connections from the deprived eye.

This dramatic shift of ocular dominance following monocular deprivation, can be recovered by patching the normal eye within the critical period, this reverse patching procedure, completely restores normal cortical organization in young kittens (Blakemore & Van Sluyters, 1974), while, after the closure of the critical period, reverse patching has only a very limited effect (Wiesel & Hubel, 1965b), suggesting that experience-dependent plasticity is limited during adulthood. Competition between monocular inputs seems to be a crucial factor driving the plastic changes observed during the critical period. Binocular deprivation, in fact has been demonstrated to have less severe consequences on primary visual cortex organization (Figure 3.1.2.C), with ocular dominance of binocularly deprived kittens being similar to normal (Wiesel & Hubel, 1965a).

Hubel and Wiesel (1970) thoroughly investigated the timecourse of ocular dominance plasticity in kittens, and found that susceptibility of primary visual cortex to the effect of monocular deprivation starts at around 3-4 weeks of age, it then peaks at around 6-8 weeks, when even a few days of monocular deprivation produce a large shift of ocular dominance in favour of the normal eye. After the peak sensitivity, experience-dependent plasticity slowly declines until 3 months of age, when the critical period ends. Importantly, the onset of the critical period can be delayed by rearing animals in the darkness, dark rearing results in slowing the timecourse of the critical period, showing that visual experience is necessary to trigger neuroplasticity (Mower, 1991). After the closure of the critical period, even prolonged periods (up to one year) of monocular deprivation do not affect ocular dominance organization (Hubel & Wiesel, 1970). We will discuss residual adult plasticity later in a dedicated paragraph.

3.1.1.2. Critical Period Regulation.

As detailed in the previous paragraph, the critical period for ocular dominance plasticity follows a well-defined timecourse that is definite for every specie. What are the factors determining the onset and the closure of the critical period?

The current understanding of the neural and molecular mechanisms controlling critical periods has been obtained from experiments on the primary visual cortex of mice, for using transgenic mice is a powerful method to investigate the molecular and cellular components underlying critical periods regulation. Another advantage of studying ocular dominance plasticity in mice is that their critical period is much shorter than that of superior mammals (see paragraph 3.1.1.), occurring between postnatal day 28 and postnatal day 32 (Gordon & Stryker, 1996), so that even few days of monocular deprivation are sufficient to generate ocular dominance re-organization, speeding up the times of research. Since the beginning of the use of transgenic mice for the study of ocular dominance plasticity, several important discoveries have been made about critical period regulation. Here we will focus on the role of balance between intracortical inhibition and excitation, that seems to be one of the most important factors underpinning the timecourse of neuroplasticity.

The first evidence revealing that the balance between excitation and inhibition is important for the modulation of ocular dominance plasticity was the discovery that the development of GABAergic inhibition was necessary to trigger the onset of the sensitive period. Hensch et al (1998) demonstrated that ocular dominance plasticity could not be induced in transgenic mice in which the GABA-synthesizing enzyme glutamic decarboxylase (GAD665) had been deleted, reducing therefore the synthesis of GABA. Interestingly, in these mice, independently of their age (so even during adulthood) the critical period for ocular dominance could not be restored until they were treated with benzodiazepines that are GABAA receptors agonists (Hensch et al., 1998). Similarly, in normal mice, the treatment with benzodiazepines can anticipate the onset of the critical period, supporting the hypothesis that an inhibitory threshold must be reached to initiate the sensitive period (Fagiolini & Hensch, 2000). Importantly, the precocious critical period produced by the injection of benzodiazepines is not observed in mutant mice whose GABAA receptors alpha1 subunits have been rendered insensitive to benzodiazepines, suggesting a precise role of inhibitory interneurons (fast-spiking Parvalbumim expressing basket cells) in mediating critical period onset (Fagiolini et al., 2004).

In line with these results, transgenic mice over-expressing the neural growth factor BDNF show an earlier development of inhibitory boutons compared with wild-types, that is accompanied by an anticipation of the critical period onset as well as by an acceleration of high visual acuity development (Hanover, Huang, Tonegawa, & Stryker, 1999; Huang et al., 1999). Interestingly, when these mice were reared in the dark, the usual delay of critical period onset provoked by dark rearing (Fagiolini, Pizzorusso, Berardi, Domenici, & Maffei, 1994) was not observed, and the animals presented high acuity vision (Gianfranceschi et al., 2003). Similar effects have been found for the over-expression of the insulin growth factor -1 (IGF-1) (Ciucci et al., 2007), that is known to stimulate the production of BDNF (Carro, Nunez, Busiguina, & Torres-Aleman, 2000), that in turns regulates the development of intracortical inhibition.

The evidence listed above clearly demonstrates that the onset of the critical period depends on the development of GABAergic inhibition. Recent evidence suggests that the continued maturation of inhibitory innervations is also one of the factors contributing to the closure of the critical period for ocular dominance plasticity. One way of investigating the mechanism underlying the closure of the critical period is studying which factors can re-open a critical period in adult animals. Several evidence have shown that changing the balance between inhibition and excitation in primary visual cortex can restore plasticity in adult visual cortex. For example, ocular dominance plasticity has been induced in adult rats housed in an enriched environment (Sale et al., 2007), this renewed neuroplasticity was associated with a decrease in GABAergic inhibition, through a reduction of the vescicular GABA transporter (VGAT). The importance of the reduction of intracortical inhibition in driving the reopening of the critical period in adult animals was confirmed in the same study by showing that the treatment with benzodiazepines blocked the visual cortex plastic potential in the animals exposed to the enriched environment (Sale et al., 2007).

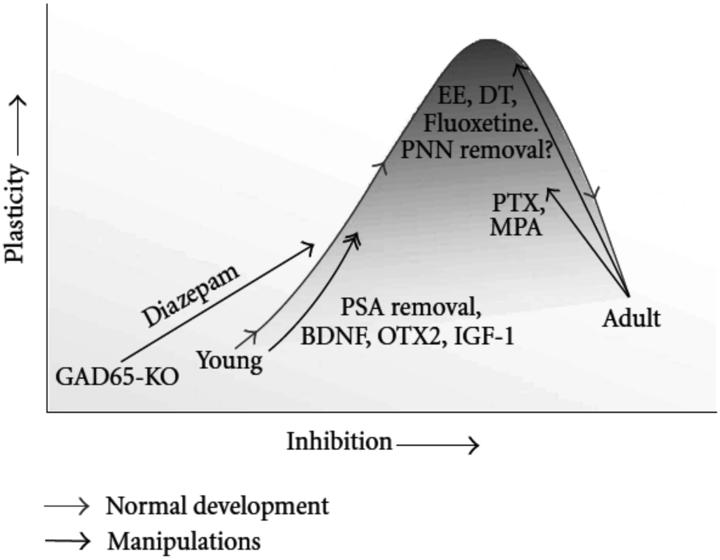

Figure 3.1.3. Inhibition and Plasticity during the critical period. Adapted from (Heimel, van Versendaal, & Levelt).
Abbreviations: EE is enriched environment, DT is dark treatment, PNN is perioneural net.

The treatment with benzodiazepine has been also shown to be effective in blocking adult ocular dominance plasticity induced by the administration of the selective serotonin reuptake inhibitor (SSRI) Fluoxetine (Maya Vetencourt et al., 2008), showing that both increasing excitation and decreasing inhibition are important for neuroplasticity. A direct evidence for decreased inhibition being one of the factors improving adult cortical plasticity was provided by Harauzov et al (2010): when the levels of intracortical inhibition were pharmacologically lowered by treating adult rats with a GABA antagonist (picrotoxin) or with an inhibitor of GABA synthesis (MPA) during monocular deprivation, ocular dominance plasticity was increased in adult animals (Harauzov et al., 2010). Moreover, by manipulating the Lynx1 protein in adult mice, Morishita et al (2010) showed that cholinergic innervations is also important for ocular dominance plasticity. When Lynx1 was removed in transgenic mice, enhancing nicotinic receptors signaling (increasing the cortical levels of cholinergic excitation), neuroplasticity was reactivated during adulthood, confirming the importance of the balance between excitatory and inhibitory circuits in regulating critical periods (Morishita, Miwa, Heintz, & Hensch, 2010). Figure 3.1.3. illustrates in a diagram the relationship between inhibition and ocular dominance plasticity.

Another factor contributing to the closure of the critical period for ocular dominance plasticity is the limitation of structural plasticity. For example, the epigenetic regulation of gene expression (ERG-CREB) has been shown to be important for neuroplasticity during the critical period, for interfering pharmacologically with this process re-opens a critical period for ocular dominance in adult animals (Putignano et al., 2007). Furthermore, removing Nogo-66 receptors results in continuation of the critical period throughout adulthood, the factor Nogo being a myelin-derived factor inhibiting axon development (McGee, Yang, Fischer, Daw, & Strittmatter, 2005). Finally, when the extracellular matrix (that blocks experience-dependent plasticity in the adult cortex by inhibiting axon and spine growth) is chemically dissolved in V1, adult animals become sensitive to monocular deprivation (Pizzorusso et al., 2002). This latter finding well illustrates how inhibitory innervations and structural plasticity are closely linked in determining neuroplasticity: a thick perioneuronal net in the extracellular matrix (forming therefore a thicker barrier for plastic changes) is in fact observed around the Parvalbumim expressing basket cells (Luth, Fischer, & Celio, 1992) that, as detailed above, are inhibitory interneurons crucial for ocular dominance plasticity. Consistently with this evidence, in transgenic mice lacking of the protein Ctrl1 (that regulates the formation of the perioneuronal nets), ocular dominance plasticity is preserved during adulthood (Carulli et al., 2010).

3.1.2. Visual cortical plasticity in the adult.

In the previous paragraph we have detailed how ocular dominance plasticity is defined and regulated during the critical period. Until recently, ocular dominance plasticity was thought to be restricted during the critical period, adult visual cortical circuits being hard-wired. However, during the last decade growing evidence has demonstrated a residual plastic potential of adult visual cortex. This has become possible because of the use of mice to study the mechanisms underlying ocular dominance plasticity, as mice, compared with other species, show a higher degree of adult plasticity (Pizzorusso et al., 2002; Sato & Stryker, 2008).

Compared to juvenile plasticity, longer periods of monocular deprivation are required to observe a shift of ocular dominance in adult animals (Blakemore, Garey, & Vital-Durand, 1978; Issa, Trachtenberg, Chapman, Zahs, & Stryker, 1999; Pham et al., 2004; Sawtell et al., 2003; Tagawa, Kanold, Majdan, & Shatz, 2005), and the shift of ocular dominance after prolonged deprivation is still smaller than that observed for shorter deprivation periods during the sensitive period. Moreover, while in young animals the ocular dominance shift occurs predominantly through a rapid depression of deprived-eye responses and in a subsequent reinforcement of the open eye responses (Frenkel & Bear, 2004; Mrsic-Flogel et al., 2007), in adult mice, the major change observed following monocular deprivation is an increase of responsiveness of the open eye (Hofer, Mrsic-Flogel, Bonhoeffer, & Hubener, 2006; Sato & Stryker, 2008; Sawtell et al., 2003).

Even if a residual ocular dominance plasticity is found in adult visual cortex, it is quantitatively and qualitatively different from that observed during the critical period, moreover, this enduring plasticity can only be observed in mice, limiting the generalization of the finding to other species. Although ocular dominance plasticity may be particularly constrained within the critical period, adult visual cortical plasticity has been reported for other properties. In the next paragraph we will review the most important discoveries regarding visual cortical plasticity during adulthood following retinal lesions, during the recovery from blindness and following prolonged visual adaptation.

3.1.2.1. Adult visual cortical plasticity following retinal lesions.

Reorganization of cortical topography has been observed in the adult visual cortex of monkeys and mice following retinal lesion. The cortical changes observed in the lesion projection zone (LPZ, that is the retinotopic region in primary visual cortex corresponding to the representation of the damaged part of the retina), after binocular lesions entail changes in receptive field properties, in molecular mechanisms and in neural circuitry (for review see Gilbert & Li, 2012). After an initial depression, the neurons within the LPZ zone regain responsiveness to visual stimulation, as a result of wide structural reorganization occurring in primary visual cortex, with neurons within the LPZ being driven by neurons in cortical regions surrounding the area representing the retinal lesion (Gilbert, Hirsch, & Wiesel, 1990; Kapadia, Ito, Gilbert, & Westheimer, 1995). This reorganization is thought to occur through the strengthening of horizontal connections that in the normal brain are thought to spread information across the visual map, allowing contour integration in primary visual cortex (Gilbert & Li, 2012).

Interestingly, the first change observed in adult rat cortex following the retinal lesion is a reduction of GABAergic inhibition (Mittmann et al., 1994), that has been shown to occur through a massive structural synaptic reorganization of GABAergic interneurons (Keck et al., 2008; Keck et al., 2011). This result points again to a leading role of the balance between intracortical inhibition and excitation in regulating visual cortical plasticity. A decrease of inhibition might be necessary for initiating experience-dependent plasticity in the adult visual cortex.

A reorganization of retinotopic maps in primary visual cortex, similar to that found for animals after retinal lesions, has been shown in humans with fMRI techniques. For example, Baker et al (2005) tested BOLD responses in two patients whose retinal fovea was damaged because of macular degeneration (Figure 3.1.4A). When measuring BOLD in the occipital cortex of these patients, that have a large binocular central retinal lesion, Baker et al (2005) found a strong activation in the foveal confluence for peripheral visual stimuli (Baker, Peli, Knouf, & Kanwisher, 2005). This result clearly indicates a large-scale reorganization of visual processing, with a big portion (20 cm^2) of deafferented visual cortex responding to visual stimuli presented in the periphery of the visual field, a reorganization that is probably due to the horizontal connections spreading information from areas receiving sensory input (those representing peripheral stimuli), to areas deprived because of macular degeneration (the foveal confluence, that, because of the cortical magnification factor for human foveal retina (Sereno et al., 1995), is a large portion of the visual cortex). Interestingly, in macular degeneration patients, the portion of visual cortex activated by peripheral visual stimuli was silent for central visual stimulation, while in normal control subjects the opposite held (Figure 3.1.4A): the foveal confluence was activated during central visual stimulation and silent during peripheral visual stimulation (Baker, Peli, Knouf, & Kanwisher, 2005).

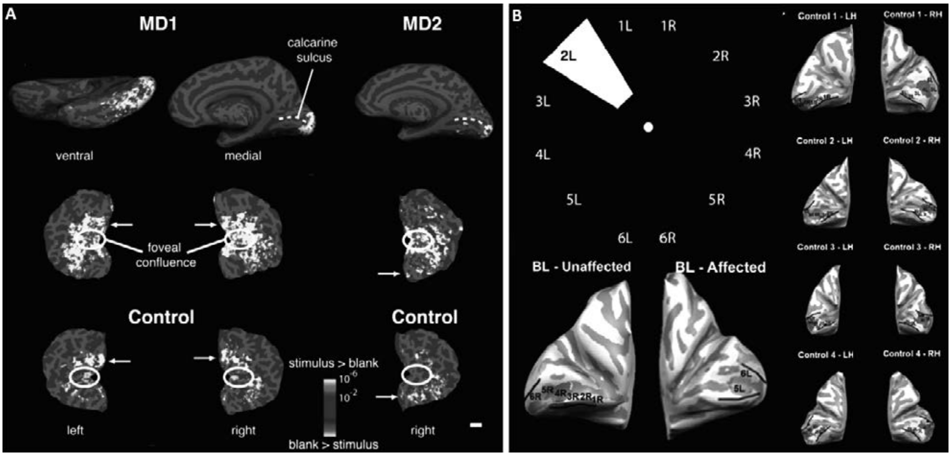

Figure 3.1.4. Topographic reorganization of adult human visual cortex following retinal lesion and stroke.

(A) Adapted from (C. I. Baker, Peli, Knouf, & Kanwisher, 2005). BOLD activation of two macular degeneration patients (MD1 and MD2) visual cortex to visual stimuli presented in the periphery of the visual field, compared with a group of control normally sighted subjects. In controls, peripheral stimulation did not activate the large portion of the visual cortex that responds to foveal stimulation (foveal confluence), that was instead activated in macular degeneration patients.

(B) Adapted from (Dilks, Serences, Rosenau, Yantis, & McCloskey, 2007). fMRI retinotopic mapping of four control subjects and one patient that had the portion of the right primary visual cortex representing the upper left visual field deafferented following a stroke. The deafferented cortex was activated by stimuli presented to the lower left visual field.

A reorganization of adult visual cortex was also reported By Dilks et al (2007) in a patient in which a stroke impaired the fibers that provide input to the region of the primary visual cortex that represents the upper left visual field (Dilks, Serences, Rosenau, Yantis, & McCloskey, 2007), as a result, the patient was blind in that part of the visual field. During a preliminary test, the authors noticed that the patient reported a distorted perception: stimuli presented to the lower left visual field appeared elongated towards the blind upper visual field, indicating that the deafferented region of the primary visual cortex was responding to stimuli presented to the adjacent lower visual field. To test this hypothesis Dilks et al (2007) performed a standard fMRI retinotopic mapping in primary visual cortex, and found that the large area of V1 that normally responds to visual stimulation in the upper left visual field was activated by stimuli presented in the lower left visual field, clearly demonstrating a plastic rearrangement of primary visual cortex organization (Figure 3.1.4B). Taken together, these results demonstrate a plastic large-scale reorganization of adult visual cortex both in animals and humans following visual cortex deafferentation due to retinal or neural injury and challenge the view that considers neuroplasticity as a property limited to the sensitive period.

3.1.2.2. Young and Adult visual cortical plasticity during recovery from blindness.

In the previous paragraphs we have reviewed experimental evidence describing the existence of critical periods early in life, that is a precise temporal window during which the visual cortex of mammals is extremely plastic: even a short period of visual deprivation occurring during the critical period causes a permanent damage to the visual cortex organization. The critical period does not end abruptly, but it rather gradually closes, with longer periods of deprivation being necessary to cause visual cortical reorganization, for this reason, the critical period is now often defined as *sensitive period* (in the previous paragraphs, in fact, we have used the two terms indifferently, for review see Elman et al., 1996). As anticipated before, it is now clear that there is not one single sensitive period for vision: different visual capabilities show different sensitive periods, i.e. different duration for experience-dependent normal development and plasticity (Blakemore, 1988; Harwerth, Smith, Duncan, Crawford, & von Noorden, 1986; W. Singer, 1988). For example, in the monkey's brain different sensitive periods have been found for scotopic and photopic sensitivity (3 months and 6 months respectively), for spatial contrast sensitivity (18-24 months) and binocularity (up to 2 years), Harwerth, Smith, Duncan, Crawford, & von Noorden, 1986.

Not only different aspects of vision show different sensitive periods, but they also follow different developmental timecourses. At birth, infant humans possess only limited visual capabilities: they can only see low spatial frequencies (0.75 cpd) and some colours, they can discriminate between round and straight countours and between orthogonal orientations, they can detect a face-like pattern and, finally, they can distinguish biological motion from scrambled motion (Adams, Maurer, & Davis, 1986; Atkinson, Hood, Wattam-Bell, Anker, & Tricklebank, 1988; Fantz, 1963; Fantz, Ordy, & Udelf, 1962; Simion, Regolin, & Bulf, 2008; Slater, Morison, & Somers, 1988). During the first 6 months of life, vision improves rapidly, so that colour vision reaches adult-like levels and acuity improves fivefold (Franklin & Davies, 2004; Maurer & Lewis, 2001a, , 2001b). In the next paragraphs we will detail the developmental timecourses as well as the sensitive periods for different aspects of vision, the two, in fact have been proposed to be closely related. The "Detroit model" proposed by Levi (1993), claims that there is a direct relationship between the developmental pace of a visual capability and its susceptibility to the detrimental effects of visual deprivation, according to the principle borrowed from economics that "first hired, last fired". According to the Detroit model the faster an aspect of vision develops, the less it will suffer from abnormal visual experience (Levi & Carkeet, 1993).

Sensitive periods have been mostly studied n animals, for depriving children of visual information is forbidden for obvious ethical reasons. A natural experiment allowing the investigation of sensitive periods in humans is provided by congenital and developmental cataract, a treatable visual disease due to a clouding of the crystalline lens. Testing children surgically treated (by replacing the opaque crystalline lens with a contact lens having an adequate refractive power) for unilateral or bilateral cataracts dense enough to block all patterned vision to reach the retina is a unique opportunity to study the effects of visual deprivation on the development of different aspects of vision. From studies involving children treated for congenital or developmental cataracts three different kinds of sensitive periods emerged: the *sensitive period of visually driven normal development* (the period during which visual input drives the normal development of the visual cortex), the *sensitive period for damage* (the period during which the visual system is vulnerable to the effects of visual deprivation, this period can occur even after that normal development is achieved) and the *sensitive period for recovery* (the period when the visual cortex can recover from the effects of visual deprivation), Lewis & Maurer, 2005.

Another interesting aspect that can be investigated by studying changes in visual capabilities in patients treated for cataracts is the role of competitive interactions between the eyes in mediating different aspects of vision. Confronting the effect of bilateral versus unilateral cataracts, in fact, allows the investigation in humans of the effects of monocular and binocular deprivation. As anticipated in the previous paragraphs, animal studies have demonstrated that monocular deprivation provokes more severe damages on the primary visual cortex organization than binocular deprivation, with a severe rearrangement of cortical connectivity being observed after monocular deprivation in which the deprived eye loses the ability of driving cortical neuronal activity (Blakemore, 1988; Crawford, Pesch, von Noorden, Harwerth, & Smith, 1991; Harwerth, Smith, Paul, Crawford, & von Noorden, 1991; Hubel, Wiesel, & LeVay, 1977; LeVay, Wiesel, & Hubel, 1980; Wiesel & Hubel, 1965a). This has been interpreted as being the result of uneven competition between the weak signal of the deprived eye with the strong signal from the fellow non-deprived eye during and after deprivation, with probably Hebbian competition underlying the pruning of deprived eye synapses (Maurer & Lewis, 2001b). In animals, the consequences of this uneven competition between the signals of the two eyes can be reduced by depriving the fellow eye during the sensitive period (Blakemore, Garey, & Vital-Durand, 1978; Wiesel & Hubel, 1965b), similarly, children treated for unilateral cataract undergo extensive patching of the "good" eye after the surgery and throughout the first 5-7 years of life.

In the next paragraphs we will review experimental evidence on young and older children, as well as adults treated for cataracts, describing the effects of visual deprivation on different visual capabilities and determining the different sensitive periods for those capabilities. We will also compare the effects of unilateral versus bilateral visual deprivation on different aspects of vision, examinig the importance of competition between the eyes for those aspects.

3.1.2.2.1. Effects of early visual deprivation on the development of basic visual capabilities: visual acuity and contrast sensitivity.

Infants' contrast sensitivity and acuity is very poor: newborns' acuity is 40 times worse than adults'. After a rapid improvement during the first six months of life, visual acuity increases more slowly during the next 4 years of life (Figure 3.1.5A) and does not reach adult levels until 6-7 years of age (Figure 3.1.5B), Ellemberg, Lewis, Liu, & Maurer, 1999; Mayer et al., 1995; Mayer & Dobson, 1982. A method to investigate visual contrast sensitivity and acuity in babies is that of “preferential looking”, that takes advantage of the fact that infants prefer to look at something patterned rather than at uniform images. The method consists in presenting contemporaneously in front of the baby two displays, one containing a grating of a certain contrast and spatial frequency, the other containing a uniform grey background of the same mean luminance. From a hole under the displays the experimenter (who is unaware of which of the two displays contains the patterned image) takes note of the time spent by the baby looking at one or the other image. The contrast and spatial frequency of the grating are varied until the infant shows no preference for one or the other display, indicating that he cannot discriminate the grating from the uniform background (Mayer et al., 1995; Mayer & Dobson, 1982).

The scarce visual acuity at birth (newborns cannot discriminate spatial frequencies higher than 1 cpd), is thought to reflect the immaturity of the retinal cones, with the rapid improvement found during the first 6 months of life likely due to the development of cones in the fovea (Banks & Bennett, 1988; Candy & Banks, 1999). The subsequent slow development of normal contrast sensitivity during childhood is thought instead to reflect the refinement of retinal and cortical connectivity and general visual cortical architecture (Huttenlocher, 1984; Huttenlocher, de Courten, Garey, & Van der Loos, 1982; Kiorpes, Kiper, O'Keefe, Cavanaugh, & Movshon, 1998).

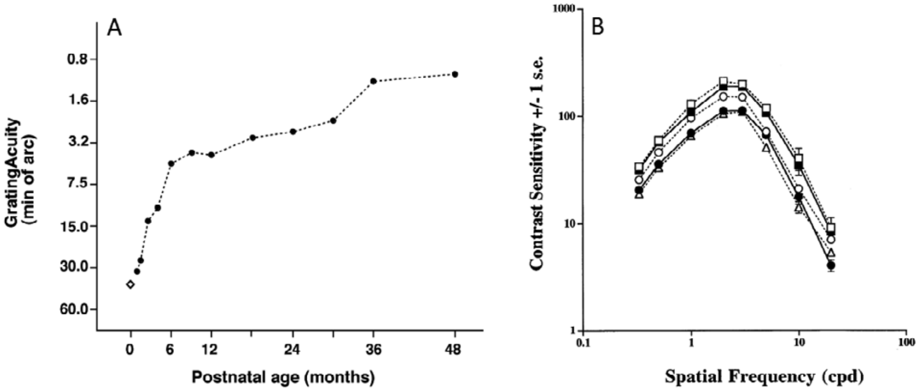

Figure 3.1.5. The development of visual acuity and contrast sensitivity during infancy and childhood. Adapted from (Ellemberg, Lewis, Liu, & Maurer, 1999).
(A) Development of visual grating acuity tested with the method of preferential looking from birth to 48 months of age, reviewed in (Maurer & Lewis, 2001a), from which the figure is adapted. (B) Changes in contrast sensitivity from the 4 to 7 years of age. The development of normal contrast sensitivity is achieved at 7 years of age.

Maurer et al (1999) found that soon after the removal of congenital bilateral cataracts (10 minutes after the restoration of vision following surgery), patients’ visual acuity in both eyes was similar to that of newborns, independently from the patients’ age, that ranged from 1 to 9 months (Maurer, Lewis, Brent, & Levin, 1999), and was therefore worse than the aged-matched control babies. This results indicates that the rapid increase of visual acuity occurring during the first 6 months of life is driven by the visual input. Interestingly, a rapid improvement was observed 1 hour following the end of visual deprivation, with patients' visual acuity reaching the level of typical 6-weeks old infants, confirming the importance of patterned visual input in driving the development of visual acuity. This results indicate that the visual system was not quiescent during visual deprivation, it is possible that, in infants with congenital cataracts, spontaneous retinal activity (for review see Katz & Shatz, 1996) is sufficient to preserve the cortical network implied in grating acuity. Furthermore, the rapid increase of visual acuity observed within 1 hour from restoration of vision indicates that the cortical neurons are ready to respond to the visually driven activity (Maurer, Lewis, Brent, & Levin, 1999).

Despite the incredibly rapid initial improvement in visual acuity shown by infants treated for congenital cataracts, longitudinal studies (Ellemberg, Lewis, Maurer, Lui, & Brent, 1999; Lewis, Maurer, & Brent, 1995; Maurer, Ellemberg, & Lewis, 2006; Mioche & Perenin, 1986) on those patients revealed that the improvement involves solely low spatial frequencies (that recover contrast sensitivity to the level of normal control group), while sensitivity to mid and high spatial frequencies does not increase after the initial enhancement (Figure 3.1.6A). Contrast sensitivity to high spatial frequencies in 5 years old children treated for congenital cataracts is even not measurable (Ellemberg, Lewis, Maurer, & Brent, 2000). This result was also confirmed for letter acuity, that shows an asymptotic deficit in patients treated for congenital cataracts (Birch, Stager, Leffler, & Weakley, 1998). The only case in which a complete recovery of contrast sensitivity to higher spatial frequencies (and therefore of visual acuity) is observed for children treated for congenital cataracts within the first 10 days of life (Kugelberg, 1992; Lundvall & Kugelberg, 2002). That sensitivity to low spatial frequencies is spared after early visual deprivation is in line with the predictions of the Detroit model, for low spatial frequencies are the only spatial frequencies visible at birth, sensitivity to higher spatial frequencies developing later. The Detroit model also holds for other basic aspects of vision. For example, critical flicker fusion, that reaches adult-like levels as early as two months of age (Regal, 1981) is preserved in children treated for congenital cataracts (Ellemberg, Lewis, Maurer, & Brent, 2000; Ellemberg, Lewis, Maurer, Lui, & Brent, 1999).

That children treated for congenital cataracts early in life (within the first 9 months of age), later show a deficit in high spatial frequency sensitivity is surprising, for the deprivation occurred well earlier than the time at which sensitivity to higher spatial frequencies matures. These phenomena are called "sleeper effects" (Maurer, Mondloch, & Lewis, 2007), and indicate that patterned vision during the first few months of life is crucial to set up the cortical neural architecture that will be finely tuned later in life. Moreover, these sleeper effects are likely to reflect deficits arising at the level of primary visual cortex: neurons in monkey's primary visual cortex show sluggish responses and anomalous receptive fields (larger than normal) after binocular deprivation, cortical damage being even more severe if monkeys were monocularly deprived. In contrast, the same deprived monkeys show normal retinal and thalamical responses (Blakemore & Vital-Durand, 1983; Crawford, Blake, Cool, & von Noorden, 1975; Crawford, Pesch, von Noorden, Harwerth, & Smith, 1991).

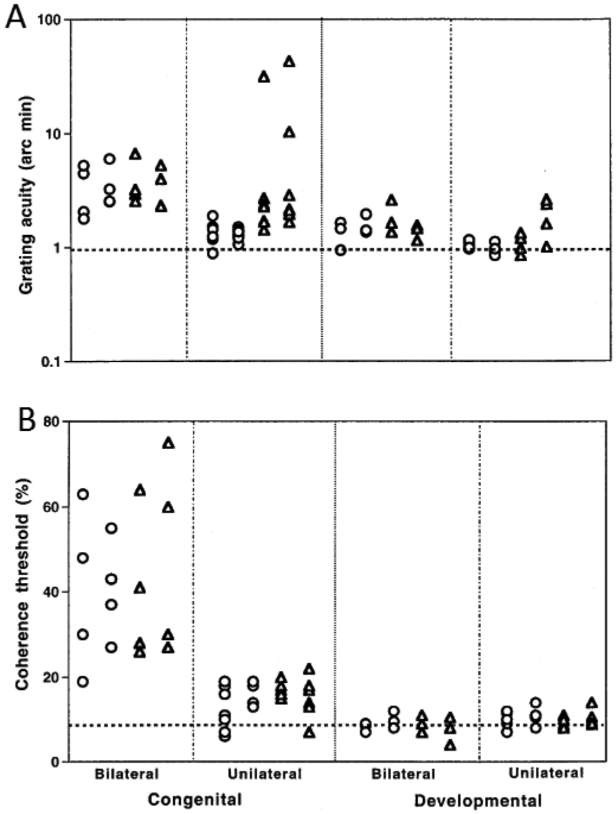

Figure 3.1.6. Grating acuity and sensitivity to global motion following treatment for unilateral and bilateral cataracts. Adapted from (Ellemberg, Lewis, Maurer, Brar, & Brent, 2002)
(A) Grating acuity following the removal of unilateral or bilateral congenital and developmental cataracts. The dashed line represents the average acuity of a control group of normal observers.
(B) Coherence thresholds for global motion discrimination following the removal of unilateral or bilateral congenital and developmental cataracts. The dashed line represents the average acuity of a control group of normal observers.

More insight about sensitive periods in humans comes from studies on developmental cataracts, that is, children having an early history of normal vision that developed dense cataract after the first 3 months of life (Lewis & Maurer, 2005; Maurer & Lewis, 2001a, , 2001b; Vaegan & Taylor, 1979). Interestingly, after treatment these patients show a better grating acuity compared with patients treated for congenital cataracts (Figure 3.1.6A), even though, only the few of them that had a very late onset of the disease (more than 11 years of age), showed normal visual acuity. This result indicates that visual deprivation occurring before 5 years of age provokes permanent deficits to grating acuity. The sensitive period for damage is even longer for letter acuity: asymptotic letter acuity is impaired for visual deprivation starting as late as 10 years of age. Regarding the sensitive period for recovery, longitudinal studies on children treated for congenital cataracts (Ellemberg, Lewis, Maurer, Lui, & Brent, 1999; Lewis, Ellemberg, Maurer, & Brent, 2000; Magnusson, Abrahamsson, & Sjostrand, 2002), demonstrated that, between 5 and 7 years of age, recovery for grating and letter acuity was still possible.

What role does competition between the eyes play in the development of basic visual properties? As anticipated in the previous paragraph, children treated for dense unilateral cataract undergo aggressive patching of the fellow eye (50 to 90% of the waking time until 5-7 years of age) in order to compensate for the uneven competition between the two eyes provoked by monocular deprivation. As expected from the evidence obtained in animal studies, children treated for monocular cataracts show worse deficits in spatial vision compared to children treated for bilateral cataracts (Figure 3.1.6A), deficits that are inversely correlated with the time of patching of the fellow eye, though, even the most aggressive patching could not completely restore vision in the deprived eye when unilateral visual deprivation occurred during the first two months of life (Jeffrey, Birch, Stager, Stager, & Weakley, 2001). These deficits include: grating acuity during infancy, asymptotic acuity and contrast sensitivity (Ellemberg, Lewis, Maurer, & Brent, 2000; Lewis, Maurer, & Brent, 1995; Lundvall & Kugelberg, 2002; Mayer, Moore, & Robb, 1989; Tytla, Maurer, Lewis, & Brent, 1988). Moreover, among the good patchers, visual acuity and contrast sensitivity was better in children treated earlier in life (Birch, Stager, Leffler, & Weakley, 1998; Birch & Stager, 1996; Birch, Swanson, Stager, Woody, & Everett, 1993).

Interestingly, the different severity of the visual deficits observed for unilateral deprivation compared to bilateral deprivation does not appear until the first year of age (Lewis, Maurer, & Brent, 1995; Mayer, Moore, & Robb, 1989). During the first month after restoration of vision, in fact, the recovery in visual acuity observed for patients treated for unilateral cataracts is comparable with that observed for patients treated for bilateral cataracts (Maurer, Lewis, Brent, & Levin, 1999), suggesting that the competitive interactions in primary visual cortex start to recover at around one year of age. Moreover, the sensitive period for damage observed in patients treated for unilateral cataracts is similar of that observed for binocular deprivation. Finally, deficits in spatial vision due uneven competition between the eyes caused by unilateral cataract have also been found in the fellow eye, that show a slightly worse visual acuity and contrast sensitivity than normal (Ellemberg, Lewis, Maurer, & Brent, 2000; Lewis, Maurer, Tytla, Bowering, & Brent, 1992; McCulloch & Skarf, 1994; Thompson, Moller, Russell-Eggitt, & Kriss, 1996). Taken together, these results indicate that balanced activity of both eyes during the first months of life is necessary for the development of optimal visual acuity.

3.1.2.2.2. Effects of early visual deprivation on the development of high level visual capabilities: global motion and global form sensitivity.

In the previous paragraph we have reviewed experimental evidence regarding the effects of early visual deprivation on basic visual features that are processed in primary visual cortex. How does early visual deprivation affect activity of higher level visual areas? In this paragraph we will focus on experiments showing how sensitivity to global motion and global form changes in patients treated for bilateral or unilateral cataracts early in life.

Sensitivity to the direction of global motion requires the integration of local motion signals (processed in primary visual cortex) over space and time, this process requires the activity of extrastriate visual areas, including the motion-sensitive middle temporal (MT) extrastriate cortex (Maunsell & Newsome, 1987; Newsome & Pare, 1988), that is connected with V1 and projects to higher level areas of the superior temporal and ventral intraparietal cortex (Ungerleider & Desimone, 1986). One efficient way to test sensitivity to the direction of global motion is using random dots kinetograms (Newsome & Pare, 1988), in which the observer has to judge the global direction of motion in a display containing dots randomly positioned with only a part of them moving in a coherent direction, the others moving in random directions (Figure 3.1.7A). To do the task the observer must integrate local motion signals over the visual field. The proportion of coherently moving dots is varied until a "coherence threshold" is found, that is the minimum proportion of coherently moving dots needed to discriminate the direction of global motion. In normal children, coherent thresholds at 6 weeks of age are 36% (Banton & Bertenthal, 1996), sensitivity then improves over years, reaching adult-like values at around 6 years of age for dots moving at high speed (Ellemberg, Lewis, Maurer, Brar, & Brent, 2002), while for dots moving at lower speed mature sensitivity to the direction of global motion is not reached until the age of 10-11 years (Ellemberg et al., 2004; Gunn et al., 2002).

In children treated for bilateral congenital cataracts the perception of global motion is highly compromised, these patients in fact show coherence thresholds 5 times higher than control normal subjects (Figure 3.1.7A, Figure3.1.6B), indicating that normal visual experience during the first 5 months of life (the average time of deprivation in this group of patients) is necessary to develop sensitivity to the direction of global motion (Ellemberg, Lewis, Maurer, Brar, & Brent, 2002). This, again, is a sleeper effect, for normal development of global motion perception occurs well after the deprivation time sufficient to produce permanent alterations. That early normal experience is crucial for the development of sensitivity to global motion was confirmed by testing patients who developed dense bilateral cataracts later in life, with a deprivation onset starting from 3 months of age. These patients in fact showed normal coherence thresholds (Figure 3.1.7A), despite the abnormal visual acuity (Figure3.1.6A), Ellemberg, Lewis, Maurer, Brar, & Brent, 2002. These results indicate that the sensitive period for damage for sensitivity to global motion is very short, with deprivation starting as soon as 3 months of age leaving coherence thresholds unaltered.

Interestingly, the impairment in sensitivity to the direction of global motion was much smaller (3-fold) in patients treated for congenital unilateral cataracts, compared with patients treated for bilateral congenital cataracts (Figure 3.1.7A), and a similar result was obtained for sensitivity to global form (Figure 3.1.7B), a visual capability that is thought to be processed in the extrastriate area V4 (H.R. Wilson, 1999), even though in the case of global form, thresholds for monocular deprivation were only 1.6 times smaller than those for binocular deprivation (Lewis et al., 2002). These results indicate that some aspects of vision mediated by extrastriate areas involve collaborative rather than competitive interactions between the eyes following early visual deprivation. This could be due to the fact that after the first stages of visual analysis (primary visual cortex), information about the eye of origin is not preserved, and inputs from the two eyes converge, for in those higher level visual areas large portions of the visual field are represented, cortical neurons having large receptive fields. Moreover, the deficits found in patients treated for bilateral congenital cataracts were less severe for global form compared to global motion perception, showing that, for high-level aspects of vision the Detroit model (Levi & Carkeet, 1993) does not hold, for sensitivity to global form show a slower developmental timecourse than sensitivity to global motion (Ellemberg, Lewis, Maurer, Brar, & Brent, 2002; Lewis et al., 2004). Therefore, according to the predictions of the Detroit model, global form perception should have been more adversely affected by visual deprivation.

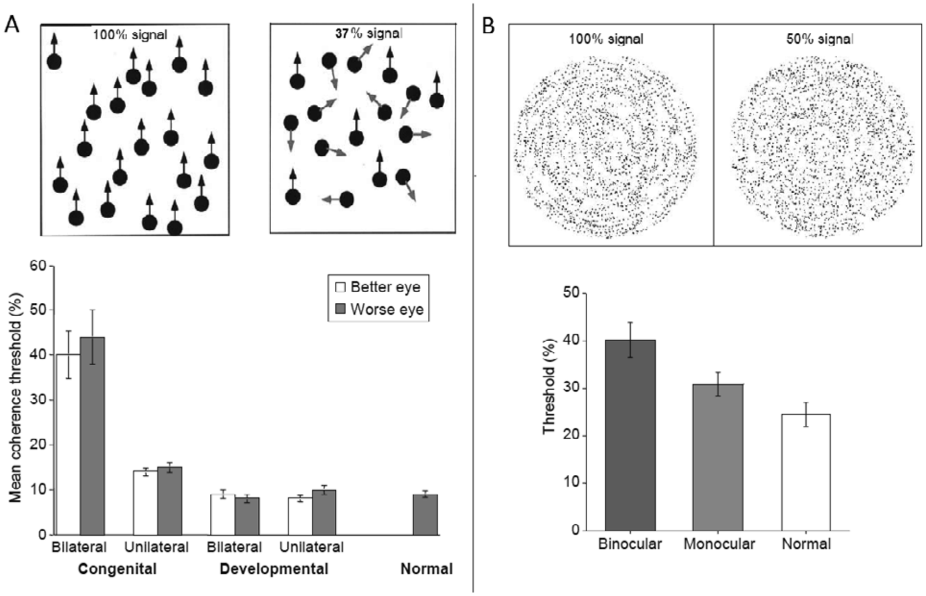

Figure 3.1.7. Sensitivity to global motion and global form in patients treated for congenital or developmental cataracts.
(A) Coherence thresholds to global motion displays in patients treated for unilateral and bilateral cataracts, if deprivation started after the first 3 months of life (developmental cataracts), patients showed normal coherence thresholds, while patients treated for binocular congenital cataracts showed abnormal global motion sensitivity. Unilateral congenital visual deprivation slightly affected sensitivity to the direction of global motion. (B) Thresholds for global form discrimination in patients treated for congenital bilateral and unilateral cataracts. After binocular deprivation sensitivity to global form was affected more severely than after monocular deprivation. Adapted from (Maurer, Lewis, & Mondloch, 2005).

In general, the experimental evidence on children treated for cataracts reviewed in the previous paragraphs clearly demonstrates that visual input during early infancy is fundamental to set up and preserve the optimal neural architecture underlying different aspects of vision. In the absence of visual input, the neurons dedicated to these visual capability may not develop properly, being pruned by Hebbian competition mechanisms eliminating the connections receiving weak inputs. Another possibility (that is not mutual exclusive with the previous one), is that the neural network dedicated to the lost aspects of vision could be recruited for the processing of other sensory modalities during the deprivation period (as detailed in the previous chapter, the visual cortex of blind patients is colonized by other sensory modalities, including audition and touch).

The developmental failure of different visual capabilities following early visual deprivation could be therefore due to the fact that the requisite neural architecture supporting them is not longer available.

3.1.2.2.3. The Project Prakash: learning to see.

Prakash in Sanskrit means “light”, that is what the Dr Shroff's Charitable Eye Hospital in New Dehli has been doing in India during the last decade in collaboration with the neuroscientist Pavan Sinha (Figure 3.1.8B): giving back light to blind children and young adults having treatable sight problems (Mandavilli, 2006). According to Orbis International (a non-profit organization), one third of the total blind people in the world live in India and because of poverty, more than 60% of those blind children die before adulthood (Mandavilli, 2006). The Prakash project restores sight performing free surgery on the congenitally blind children, the majority of which are born with corneal opacities or dense cataracts (Figure 3.1.8A). Most patients treated with the project Prakash are older than the standard patients treated for congenital cataracts and constitute a unique occasion to study the effects of prolonged visual deprivation on the development of the visual system, as well as the sensitive periods for different aspects of vision in a time window rarely explored by other studies. The first report on the Prakash project, in fact regarded a 29-years old man (subject S.K.) who regained vision thanks to the prescription of appropriate spectacles to correct his congenital aphakia (the absence of the crystalline lens, that is almost totally absorbed in the chambers).

One of the first reports from the project Prakash described the recovery of visual abilities in a 34 years old woman with an early history of dense congenital bilateral cataracts (Ostrovsky, Andalman, & Sinha, 2006). S.R.D underwent surgery at the age of 12 years, and therefore had 22 years over which she had the possibility of acquiring visual function learning to see. As expected from animal studies and evidence on children treated for cataracts (reviewed in the previous paragraphs), S.R.D. had poor visual acuity (20/200), showing that visual restoration after the end of the sensitive period does not result in the recovery of basic aspects of vision. The team guided by Pavan Sinha performed several visual tests on S.R.D. involving basic form perception (shape matching, visual memory, matching transformed shapes, depth from configural cues and image segmentation) and face perception (face/non face discrimination, face localization, face matching, gaze direction judgment and gender classification). Surprisingly, these authors found that, despite the prolonged period of visual deprivation starting from birth, S.R.D. performed as well as control normal observers in all of the visual tasks (Ostrovsky, Andalman, & Sinha, 2006). The spared visual capabilities shown by S.R.D. were the result of an extensive learning and were not available soon after surgery. This result indicates that recovery of high level visual function is still possible via learning during adulthood, demonstrating that adult visual cortex retains a high degree of neuroplasticity.

Figure 3.1.8. The Prakash Project.
(A) Adapted from (Sinha & Held, 2012). Two examples of sight disease treated by the team: corneal opacities (left panel) and dense cataracts (right panel).
(B) Adapted from (Mandavilli, 2006). Pavan Sinha testing the visual capabilities of one of the children treated in the hospital.

In another report, the visual capabilities of 3 subjects from the project Prakash has been studied longitudinally from the restoration of sight up to 18 months later (Ostrovsky, Meyers, Ganesh, Mathur, & Sinha, 2009). One of the patients tested was S.K., whose case has been described above. The other two patients were two children who underwent surgery for dense bilateral congenital cataract, one (P.B.) at the age of 7 years, the other (J.A.) at the age of 13 years. In these patients, as in the case of S.R.D. visual acuity recovered only slightly and remained very poor. The three subjects were then tested soon after surgery for high level aspects of vision: static visual parsing (counting simple shapes presented on a display), object recognition (naming 50 common objects) and dynamic visual parsing (counting simple shapes with additional motion cues). All of the subjects showed good proficiency in enumerating geometrical shapes when these were presented alone or with other non-overlapping shapes. When the different shapes presented in the same display overlapped, observers were not able to do the task and perceived all closed loops and regions of uniform luminance or color as separate objects (Figure 3.1.9A). This result indicates that patients whose vision was restored late in life (after the closure of the critical period), have a profound deficit in integrating contours into a global image, resulting in a overfragmentation of the images. Similarly, these patients also showed a poor performance in the complex objects naming task, where they perceived regions of different colors of luminance as distinct objects (Ostrovsky, Meyers, Ganesh, Mathur, & Sinha, 2009).

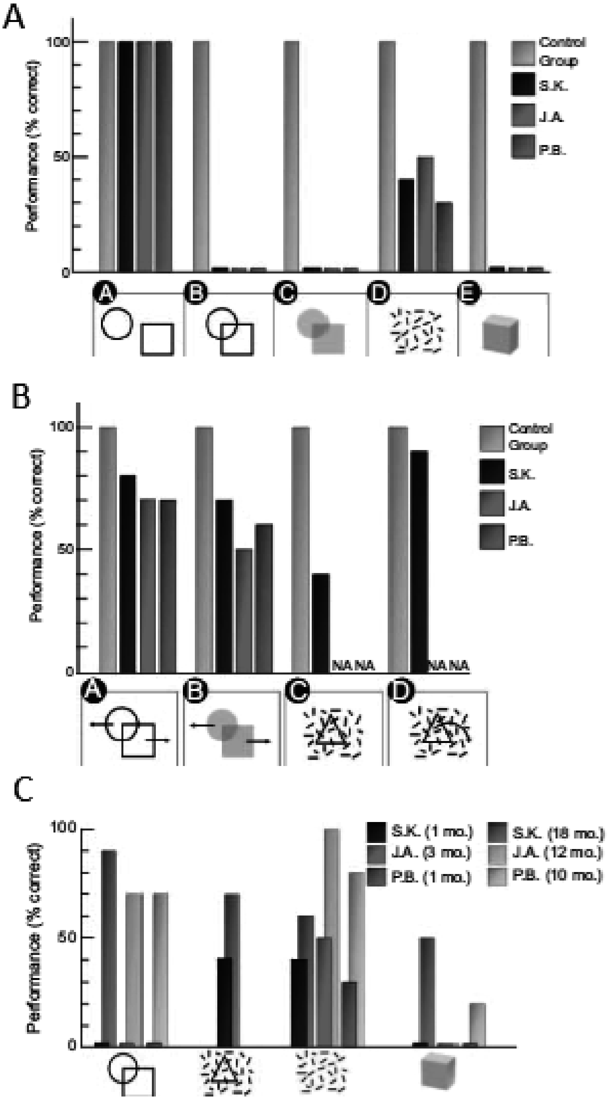

Figure 3.1.9. Visual parsing abilities of three patients from 3 up to 18 months after the restoration of vision. Adapted from (Ostrovsky, Meyers, Ganesh, Mathur, & Sinha, 2009).
(A) Patients' performance to static visual parsing tasks in which they had to count the number of objects presented on the display. When geometrical shapes overlapped subjects were unable to perform the task because they overfragmented the visual scene.
(B) Patients' performance to dynamic visual parsing tasks. Motion cues allowed correct segregation of the overlapping visual objects.
(C) Patients' performance to static visual parsing tasks measured from 10 to 18 months following visual restoration. Each of them improved in segmenting the objects, indicating that they learn this visual ability over time.

Interestingly, in the dynamic visual parsing task, where the instruction was the same as in the static visual parsing experiment (count the objects on the display), the patients responded correctly in the majority of the cases (Figure 3.1.9B), indicating that introducing motion cues enabled the correct segmentation of visual objects (Ostrovsky, Meyers, Ganesh, Mathur, & Sinha, 2009). Patients recently treated for visual disease used motion information to segregate objects from the background, while in static viewing conditions they showed a severe integrative impairment. This result is in line with a previous report by Fine et al (2003) that we will discuss in the next paragraph (Fine et al., 2003). The authors also speculate that the earlier development of motion sensitivity observed in normal children is the factor that allows the subsequent correct development of static segmentation (Ostrovsky, Meyers, Ganesh, Mathur, & Sinha, 2009).

Finally, when the same three patients were tested on static visual parsing later after restoration of vision (from 10 to 18 months), an important improvement of performance was observed for all of them (Figure 3.1.9C). This result indicates that high level visual function as object parsing was acquired by the patients later after the treatment, the delay being necessary for the subjects to "learn how to see" (Ostrovsky, Meyers, Ganesh, Mathur, & Sinha, 2009). As in the case of S.R.D., high level visual capabilities were acquired in adult subjects via learning and needed a prolonged time to recover, probably because of the more limited plasticity of adult visual cortex compared to the juvenile cortex. In any case, the evidence described above clearly questions the idea of a strict restriction of plasticity within the sensitive period, demonstrating that high level visual capabilities can be recovered via learning also during adulthood.

3.1.2.2.4. The man who learnt to see.

Almost a decade ago, Fine et al (2003) reported the outstanding case of a 43 years old man (M.M.), who reacquired vision in one eye after 40 years of deprivation (Fine et al., 2003). When he was 3 and a half years old, in fact, M.M. completely lost one eye and had a severe thermal damage to the cornea of the other eye, such that he only had some light perception in that eye, but no patterned experience. Almost 40 years later, M.M. was operated (stem-cell transplant) and recovered some vision in the right eye. Following surgery, in line with the results observed with the other patients whose vision was reacquired after prolonged deprivation, M.M. showed poor visual acuity, with spared contrast sensitivity only for low spatial frequencies (maximum visible spatial frequency at high contrast 1 cpd).

Thorough examination revealed that M.M.'s right eye retina was not damaged, suggesting a central origin of his visual impairment for mid and high spatial frequencies. This was confirmed by fMRI results: already at low spatial frequencies, BOLD responses in V1 were one fifth compared to V1 responses of control normal observers, when visual stimuli spatial frequency exceeded 1 cpd, MM's BOLD responses fell off dramatically and were near to zero. M.M.'s visual acuity was retested longitudinally for 2 years following surgery and did not improve within that time, in line with the evidence that early visual deprivation permanently impairs contrast sensitivity to mid and high spatial frequencies discussed in the previous paragraphs. The case of M.M. is however peculiar, in fact, at the age of 3 and a half years (when he became blind), his visual acuity should have been around 25 cpd, way more than the sensitivity recovered after treatment. This result indicates that prolonged deprivation had degraded M.M.'s visual cortex resolution.

When tested for higher-level visual functions (Figure 3.1.10), M.M. showed optimal performance in simple form tasks, as well as good orientation sensitivity and color perception. He had no problems in segmenting texture patterns based on luminance contrast, but showed a slight deficit in integrating texture elements into a global shape. He also could not resolve illusory contours, such as the Kanisza triangle, unless the form of the triangle was outlined. Similarly, he could not interpret prospective cues and was unable to resolve the Necker cube. In line with the results obtained with the patients of the Prakash project (Ostrovsky, Andalman, & Sinha, 2006; Ostrovsky, Meyers, Ganesh, Mathur, & Sinha, 2009), M.M. showed overfragmentation mistakes: he interpreted two geometrical shapes overlapping in transparency as three distinct objects (even though he could easily resolve occlusions), and he showed a extensive deficit in identifying common objects and unfamiliar faces (Fine et al., 2003).

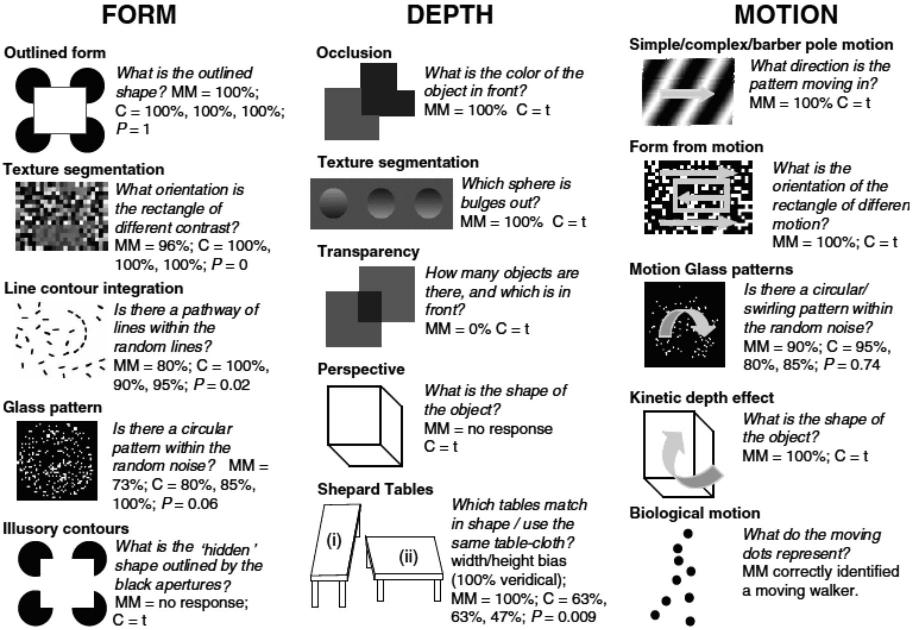

Figure 3.1.10. Psychophysical visual tasks and performance 5 months after treatment. Adapted from (Fine et al., 2003).
Three different aspects of vision were investigated administering psychophysical visual tests to the patient M.M. and a control group of normal subjects: form recognition, depth perception and motion sensitivity.

Interestingly, despite the important deficits shown in object recognition, M.M.'s performance was very good in most of the motion tasks: he could detect well the direction of simple and complex plaid motion and could segment texture patterns based on motion, as well as identifying dynamic Glass patterns from random noise. Not only he showed spared motion sensitivity per se, but he could also proficiently use motion cues to resolve transparency and three-dimensional shapes, such as the

Necker cube, that he could not resolve in static conditions. The pattern of fMRI activation to high-level visual stimuli reflected M.M.'s psychophysical performance: BOLD responses in the motion-sensitive area V5/MT were comparable to that of normal controls, while the visual areas usually devoted to the processing of faces (fusiform gyrus) and complex objects (lingual gyrus) were not activated by their usually preferred visual stimuli (Fine et al., 2003).

Taken together, the case of M.M. suggests that not only early visual deprivation (soon after birth) is important to develop normal visual function, but also visual experience beyond 3 years of age is necessary to achieve optimal visual processing. Prolonged visual deprivation starting at 3 and a half years of age caused long-lasting, if not permanent damages to visual cortical organization and resolution, with the exception of motion processing. As detailed in the previous paragraphs, motion sensitivity develops earlier than form processing, and, as predicted by the Detroit model (Levi & Carkeet, 1993), is more robust to the effect of visual deprivation, for at the age of 3 and a half years, the neural network dedicated to motion processing could be more established and hard-wired. Another possible explanation suggested by Fine et al (2003) for the pattern of visual deficits shown by M.M. is that the mechanisms underlying the analysis of complex objects could remain plastic for a longer period to allow learning of novel shapes throughout life.

3.1.2.3. Adult human cortical plasticity due to transient visual deprivation or prolonged adaptation.

In the previous paragraphs we have described how young and adult visual cortex can plastically adapt to abnormal sensory input following sensory loss the duration of which spanned from a few months to decades. Another way of approaching the study of visual cortical plasticity is that of investigating whether the adult visual system can adapt to transient modifications of the visual input, either through temporary deprivation of visual input, or via prolonged adaptation. In this paragraph we will review some recent experiments that addressed this issue and demonstrated residual plasticity of adult human visual cortex in response to transient modifications of the visual environment, such as light deprivation, contrast reduction and prolonged orientation-specific deprivation.

3.1.2.3.1. Short-term light deprivation induces plastic changes of adult human visual cortical excitability.

In 2000, Boroojerdi et al investigated whether a transitory period of light deprivation was able to modulate adult visual cortical excitability (Boroojerdi et al., 2000). Their hypotheses were that a brief period (180 minutes) of light deprivation would result in enhanced excitability and in an augmented activation in response to visual stimulation of the occipital cortex of adult human observers. To test these hypotheses, the authors directly stimulated with transcranial magnetic stimulation (TMS) and measured variation in the BOLD signal in the occipital cortex of adult participants undergoing a period of light deprivation (Boroojerdi et al., 2000).

When applied on the occipital cortex, TMS can induce the perception of flashes of light in the absence of visual stimulation, these TMS-evoked visual sensations are called "phosphenes" (Marg & Rudiak, 1994). By varying the intensity of the transcranial magnetic stimulation, one can determine the so called "phosphene threshold", that is the minimum TMS intensity necessary to elicit phosphenes. Variations in phosphene thresholds are thought to convey information about the excitability of the occipital (visual) cortex (Afra, Mascia, Gerard, Maertens de Noordhout, & Schoenen, 1998; Aurora, Ahmad, Welch, Bhardhwaj, & Ramadan, 1998). To monitor possible changes in visual cortical excitability provoked by light deprivation, Boroojerdi et al (2000), measured phosphene thresholds in adult human participants at regular intervals of 45 minutes (Figure 3.1.11A.), before, during and after a period of light deprivation (180 minutes). Importantly, in the absence of visual deprivation, phosphene thresholds tested in the same intervals did not significantly varied (Boroojerdi et al., 2000). Interestingly, a significant reduction of phosphene thresholds was observed during the deprivation period, the largest reduction occurring within the first 90 minutes (Figure 3.1.11A). To test the timecourse of phosphene thresholds recovery, Boroojerdi et al (2000) also had observers undergoing light-deprivation for 90 minutes (that is the time necessary to achieve the maximum variation in phosphene thresholds), and found that thresholds reverted to normal values at around 120 minutes following re-exposure to normal vision (Boroojerdi et al., 2000).

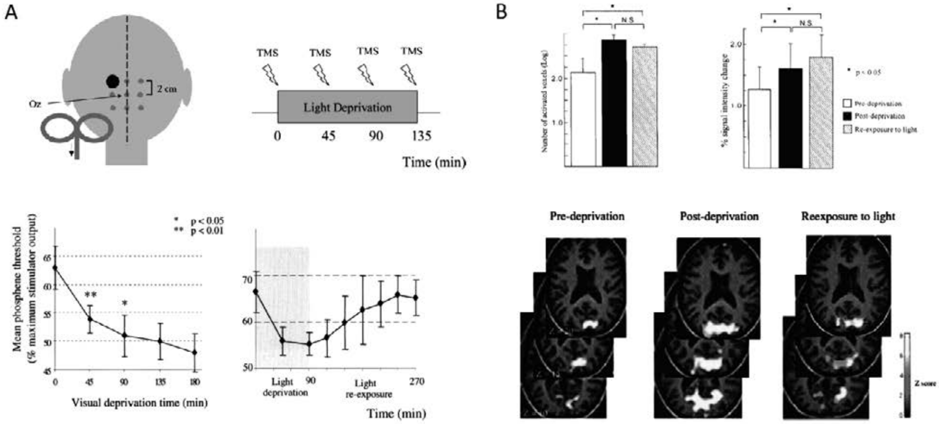

Figure 3.1.11. Changes in adult human occipital cortical excitability and activation during transient periods of light-deprivation. Adapted from (Boroojerdi et al., 2000).
(A) Diagram of the paradigm and results of the TMS experiment. Phosphene thresholds were measured during and after a period (180 or 90 minutes) of light deprivation in normal adult observers. During the first 90 minutes of light deprivation, phosphene thresholds significantly decreased and did not return to baseline levels until 120 following re-exposure to normal vision.
(B) Results of the fMRI experiment. BOLD activation was measured in the occipital cortex during and after 60 minutes of light deprivation. Both the number of voxels and the intensity of the signal in response to photopic stimulation increased after light deprivation and were still higher than baseline measurements 30 minutes after the offset of visual deprivation.

Light deprivation not only induced changes in cortical excitability that resulted in decreased phosphene thresholds, but also increased neural activity during photic stimulation, as measured by fMRI BOLD signal: after 60 minutes of light deprivation, an increase in both the number of voxels activated and in the intensity of the BOLD signal at the level of the occipital cortex (but not in LGN) was observed (Boroojerdi et al., 2000). This increased neural activation did not return to baseline 30 minutes after re-exposure to light (Figure 3.1.11B). These results indicate that the adult visual cortex still retains a form of experience-dependent plasticity, for a brief period of light deprivation is able to increase occipital cortical excitability (reflected in the decreased phosphene thresholds after deprivation) and neural activation (reflected in the augmented hemodynamic response of the occipital cortex).

In a subsequent study by the same group (Boroojerdi, Battaglia, Muellbacher, & Cohen, 2001), the mechanisms underlying this form of experience-driven plasticity were investigated by repeating the TMS experiment in adult human observers after the administration of different drugs that are known to interfere with synaptic plasticity: *lorazepam* (a benzodiazepine that increases GABAergic inhibition by acting as positive allosteric of GABAA receptors), *dextrometorphan* (a substance that blocks NMDA receptors involved in mechanisms of long term potentiation, LTP), *scopolamine* (an antagonist of acetylcholine muscarinic receptors) and *lamotrigine* (an antiepileptic that does not influence LTP, but blocks voltage-gated Na^+ and Ca^{2+} channels). Interestingly, the administration of all of these drugs, but lamotrigine, prevented the light-deprivation-induced increase of cortical excitability observed in drug-naïves observers and measured via phosphene threshold changes (Boroojerdi et al., 2000). From this result, the authors concluded that the transient neuroplasticity produced by light deprivation in adult human visual cortex is regulated at least by three different mechanisms: balance between intracortical GABAergic inhibition and cholinergic excitation, activation of NMDA receptor and mechanisms of long-term potentiation (Boroojerdi, Battaglia, Muellbacher, & Cohen, 2001). Interestingly, as detailed in the previous paragraphs, the same neural and molecular mechanisms have been found to be important for critical period regulation in animals.

3.1.2.3.2. Plastic alterations of the adult human visual cortex activity during prolonged contrast reduction.

As described in the previous paragraphs, patients with dense cataracts experience prolonged contrast deprivation, with only some spared light perception, but no pattern information reaching the retina. An interesting study by Kwon et al (2009) investigated the effects of prolonged (4 hours) exposure to contrast reduction on visual contrast sensitivity and early neural activation (BOLD signal in V1 and V2) in adult human observers (Kwon, Legge, Fang, Cheong, & He, 2009). These authors hypothesized that extended contrast reduction would cause compensatory modifications in the adult visual system, resulting in an increased response gain in visual cortex that would be reflected behaviourally in an improve of contrast discrimination thresholds.

To explore this hypothesis, Kwon et al (2009) had a group of adult observers wearing contrast-reducing goggles for 240 minutes (main experiment) and a control group of adult observers wearing neutral-density goggles for the same period of time (control experiment). Before and after the period of contrast reduction, contrast discrimination thresholds were tested in the two groups of observers for seven different contrast pedestals (0%, 0.3%, 1%, 1.6%, 3.3%, 8.3% and 16.6% of filtered contrast), in order to obtain thresholds-vs-contrast (TvC) functions (Legge & Foley, 1980; Nachmias & Sansbury, 1974). Moreover, fMRI BOLD activation in V1 and V2 was measured for the two groups of participants for different contrasts (1%, 3.3%, 8.3% and 16.6% of filtered contrast), in order to obtain neuronal contrast response functions (CRF) from the BOLD activation in early visual areas (Boynton, Demb, Glover, & Heeger, 1999; Zenger-Landolt & Heeger, 2003). Figure 3.1.12A shows a diagram of the experimental paradigm.

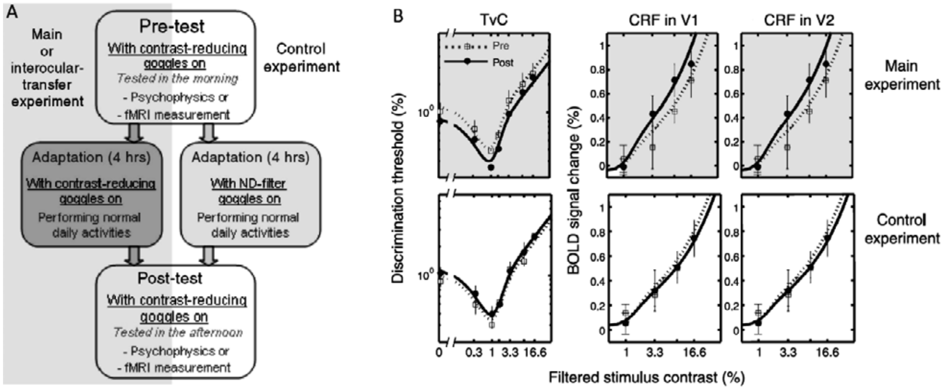

Figure 3.1.12. The effect of prolonged contrast reduction on contrast discrimination thresholds and neuronal contrast response functions in V1 and V2 of adult human observers. Adapted from (Kwon, Legge, Fang, Cheong, & He, 2009).

(A) Adult observers underwent 4 hours of exposure to low contrast in one eye, while a translucent eyepatch was worn on the other eye, before and after contrast reduction contrast discrimination thresholds and BOLD signal in V1 and V2 were measured (main experiment). A control group of subjects wore neutral filters instead of contrast reducing ones and performed the same tasks.

(B) After 4 hours of contrast reduction, contrast discrimination thresholds improved, leading to a downward shift of the TvC function and activity in V1 and V2 was enhanced for the whole range of contrasts tested (1-16.6% of filtered contrast).

The contrast-reducing filter attenuated contrast by a factor of 3 (0.5 log unit) and minimized blur, resulting in a small acuity reduction (less than 0.2 logMAR) and in a luminance reduction of a factor of 2 (0.3 log unit). The filters were created with diamond powder and casting acrylic (Pelli, 1987). The contrast-reducing goggles used in the main experiment had this contrast-reducing filter mounted over the observer's dominant eye and a translucent occluder that did not allowed patterned vision and was matched with the contrast-reducing filter for luminance attenuation mounted over the fellow eye. The neutral density filter goggles used in the control experiment were similar to the contrast-reducing goggles, but had a neutral-density filter matched in luminance attenuation with the other filters mounted over the dominant eye (Kwon, Legge, Fang, Cheong, & He, 2009). In both experiments, psychophysical and fMRI measurements were obtained with observers wearing the contrast-reducing goggles.

Figure 3.1.12B shows the psychophysical TvC functions and the neuronal CRF functions measured before and after four hours of exposure to low-contrast for the main experiment (upper panels) and for the control group wearing the neutral density goggles for the same amount of time (lower panels). Prolonged adaptation to low contrast resulted in lowered contrast discrimination thresholds and in increased fMRI BOLD activation (neuronal CRFs) compared with measurements obtained before contrast-reduction. Importantly, no difference between pre- and post-deprivation measurements was observed in the control experiment, indicating that the behavioural and neural changes observed were a consequence of the exposure to low contrast and did not depend on fatigue.

Interestingly, the pattern of results obtained was consistent with prolonged contrast reduction resulting in augmented response gain in V1 and V2. Neuronal CRFs were in fact steeper after long-term adaptation (with an increase of the maximum neural response of a factor of 1.3) and the TvC were shifted downwards, indicating improved contrast discrimination thresholds for all pedestal contrast tested (Figure 3.1.12B). Finally, the cortical origin of the observed effect was confirmed by the fact that the adaptive changes produced by prolonged adaptation to low contrast showed full interocular transfer (Kwon, Legge, Fang, Cheong, & He, 2009).

Taken together, these results indicate that the adult visual system reacts to the reduction of incoming information due to prolonged exposure to low contrast by increasing cortical response gain in order to maximize neural response to weaker visual input. These compensatory changes in adult visual cortex activity increase the evidence in favour of a residual plastic potential of adult visual cortex, more than previously thought.

3.1.2.3.3. Orientation-specific visual deprivation induces changes in visual sensitivity.

During development the visual cortex of mammals is highly vulnerable to the effects of visual deprivation. Not only ocular dominance plasticity is observed after periods of monocular deprivation, but also deprivation to a specific orientation can alter the organization of the developing visual cortex. If, during the sensitive period, kittens are reared in the dark with daily exposure only to a certain orientation (e.g. vertical or horizontal), the number of neurons in primary visual cortex responding to the deprived orientation is dramatically reduced and kittens permanently lose the ability of seeing the deprived orientation (Blakemore & Cooper, 1970; Hirsch & Spinelli, 1970; Sengpiel, Stawinski, & Bonhoeffer, 1999; Tanaka, Ribot, Imamura, & Tani, 2006). Using an innovative experimental setup, Zhang et al (2009) investigated the effects of selective deprivation to a specific orientation on visual perception of adult humans (Zhang, Bao, Kwon, He, & Engel, 2009). In this study, observers wore a head-mounted video camera feeding into a laptop, that processed online the images from the camera, filtering them in real time and driving a head-mounted display in which the filtered images of the external world were presente. In this way, observers were free to navigate and interact with the external environment. The filtering resulted in deprivation of a specific orientation, e.g. the vertical orientation as shown in Figure 3.1.13. in which a picture of the setup and the resulting natural and filtered images are reported.

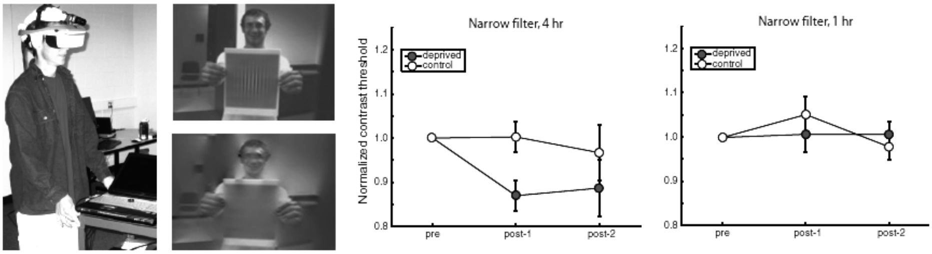

Figure 3.1.13. Orientation-specific deprivation enhances visual sensitivity to the deprived orientation. Adapted from (Zhang, Bao, Kwon, He, & Engel, 2009).
Adult participants experienced 4 hours of selective deprivation to a specific orientation, using a head-mounted display filtering online the incoming images from a head-mounted video camera. After 4 hours of selective deprivation, observers' discrimination thresholds for the deprived orientation significantly decreased during the following 40 minutes, indicating improved sensitivity. 1 hour of deprivation was ineffective in producing the performance gain observed for 4 hours of deprivation.

Interestingly, Zhang et al (2009) found that, following 4 hours of selective deprivation to a specific orientation, sensitivity to the deprived orientation significantly improved, with lower discrimination thresholds for the deprived orientation being obtained during the first 40 minutes following deprivation offset. After shorter-term (one hour) deprivation instead discrimination thresholds did not differ from baseline measurements (Figure 3.1.13.). Moreover, the improvement in sensitivity observed after 4 hours of selective deprivation went back to baseline measurements when discrimination thresholds were measured 24 hours afterwards (Zhang, Bao, Kwon, He, & Engel, 2009). These results indicate that visual deprivation to a specific orientation results in a compensatory increase in responsiveness of neurons representing the deprived orientation in early adult visual cortex.

A following study by the same group further investigated the effects of orientation-specific deprivation (Bao & Engel, 2012). In this study, the effect of orientation deprivation of different durations (1, 4 and 8 hours) on visual perception was measured by quantifying the strength and duration of the tilt aftereffect (TAE). Following deprivation (obtained with the experimental setup described above and shown in Figure 3.1.13) observers were asked to adjust the orientation of two overlapping gratings (plaid pattern) oriented at ±45°, until they appeared to be squared.

Figure 3.1.14A shows that the strength of the tilt aftereffect increased with increasing duration of deprivation, with size of the tilt aftereffect increasing in a nearly linear fashion with the logarithm of the adaptation duration (Bao & Engel, 2012). Not only the strength, but also the duration of the TAE increased for longer periods of deprivation. For the 4 and 8 hours of deprivation conditions, in fact the curves, obtained by measuring repeatedly over time the size of the TAE, asymptoted to a positive effect (Figure 3.1.14A). The timecourse of the TAE after deprivation offset was well fit both by power and exponential decay functions, for it showed a peak soon after the end of deprivation, with a rapid decay and a constant value thereafter (Figure 3.1.14A).

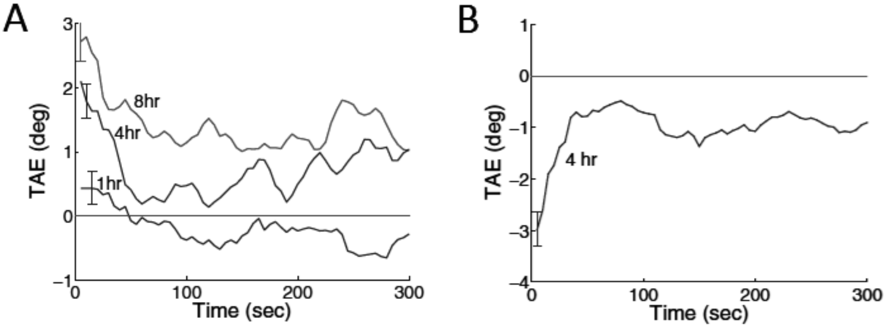

Figure 3.1.14. Deprivation and adaptation to a specific orientation show similar timecourses. Adapted from (Bao & Engel, 2012).

(A) Observers were adapted to real-world images deprived of the vertical orientation for different amounts of time (1, 4 or 8 hours). After orientation deprivation, a strong tilt aftereffect was measured: the strength and duration of the effect depended on the duration of the deprivation.

(B) Observers were adapted for 4 hours to real-world images in which the contrast of the vertical orientation was enhanced. After adaptation the measured tilt aftereffect was in the opposite direction compared with that observed for deprivation, but showed a similar dynamics, with the effect rapidly decaying over the first minute of visual stimulation and then asymptoting to a positive effect.

The authors hypothesized that the same compensatory neural mechanisms, but acting in opposite directions underpinned the effect of deprivation and adaptation. In the case of deprivation, the visual system would react by increasing neural responsiveness (gain), in order to make sure that none of the impoverished information get lost. In the case of adaptation, instead, the same mechanisms would decrease neural gain in order to avoid response saturation to highly contrasted visual stimulation. In both cases, this mechanism would allow the accurate signaling of small changes in environmental contrast. To test this hypothesis, Bao & Engel (2012) tested the tilt aftereffect after 4 hours of prolonged adaptation to enhanced contrast of a specific orientation with the same altered reality setup. They found that prolonged adaptation to high contrast vertical orientations resulted in a robust TAE (in the opposite direction compared to the deprivation-induced TAE) that decayed to a positive asymptote with a dynamics extremely similar to that observed for orientation-specific deprivation (Figure 3.1.14B), confirming the hypothesis that same neural mechanisms underlie the two phenomena (Bao & Engel, 2012). Finally, the effect of 4 hours of deprivation was also found to vanish after 15 minutes of exposure to normal visual scenes (deadaptation). Interestingly, the effect of deprivation, annulled by the deadaptation, was fully restored by exposing observers to only 8 minutes of orientation-selective deprivation. The authors interpreted these results as an evidence in favour of two distinct mechanisms operating for short-term and long-term visual adaptation (Bao & Engel, 2012).

Taken together, the results described in this paragraph demonstrate that the adult human visual cortex retains a high degree of experience-driven plasticity that operate also in response of selective deprivation of a specific orientation. Moreover, these findings reinforce the evidence in favour of a compensatory reaction of the adult visual system to the lack of information, that results in an increased responsiveness of the neurons whose input had been impoverished in order to compensate for the signal attenuation and optimally convey the visual information surviving deprivation.

In the next paragraphs we will present two experimental studies in which we used binocular rivalry as a tool to investigate residual neuroplasticity of the adult human visual system after short-term visual deprivation in one eye.

In the first study we found that, after 150 minutes of monocular deprivation, visual perception during binocular rivalry was strongly biased in favour of the deprived eye, with an effect on the onset of rivalry being measurable for up to 90 minutes following re-exposure to normal binocular vision. Moreover, by testing apparent contrast before and after the same patching procedure, we also showed that following monocular deprivation stimuli presented to the previously deprived eye appeared to be stronger than stimuli presented to the non-deprived eye by a factor of 1.36.

In the second study we expanded the results obtained in the first report by showing that the effect of monocular deprivation on the dynamics of binocular rivalry is stronger and more long-lasting when chromatic rather than luminance-modulated gratings are tested, with an effect on sustained rivalry being measurable for up to 180 minutes following eyepatch removal.

Finally, we will also present some preliminary data from an experiment in which we measured binocular rivalry in amblyopic children during five months of occlusion therapy. These preliminary report indicates that binocular rivalry can be efficiently used as a tool to monitor neuroplasticity during the recovery of visual function in the amblyopic eye driven by the occlusion of the fellow eye.

3.2. Brief periods of monocular deprivation disrupt ocular balance in human adult visual cortex.

Neuroplasticity is a fundamental property of the developing mammalian visual system, with residual potential in adult human cortex (Karni & Bertini, 1997). A short period of abnormal visual experience (such as occlusion of one eye) before closure of the *critical period* has dramatic and permanent neural consequences, reshaping visual cortical organization in favour of the non-deprived eye (Berardi, Pizzorusso, & Maffei, 2000; Wiesel & Hubel, 1963b). We used *binocular* rivalry (Tong, Meng, & Blake, 2006) – a sensitive probe of neural competition – to demonstrate that adult human visual cortex retains a surprisingly high degree of neural plasticity, with important perceptual consequences. 150 minutes of monocular deprivation strongly affected the dynamics of binocular rivalry, unexpectedly causing the *deprived eye* to prevail in conscious perception twice as much as the non-deprived eye, with significant effects for up to 90 minutes. Apparent contrast of stimuli presented to the deprived eye was also increased, suggesting that the deprivation acts by up-regulation of cortical *gain-control* mechanisms of the deprived eye. The results suggest that adult visual cortex retains a good deal of plasticity that could be important in reaction to sensory loss.

3.2.1. Results and Discussion

We investigated the effects of monocular deprivation on the dynamics of *binocular rivalry* in adult humans. Seven observers wore a translucent eye-patch on one eye for 150 minutes, then viewed a dichoptic binocular-rivalry display with horizontal grating patches presented to one eye and vertical to the other (Figure 3.2.1a), reporting by continuous key-press which pattern they perceived. Figure 3.2.1*b* shows the effect of monocular deprivation on the phase durations during rivalry, separately for the deprived (black symbols) and non-deprived (orange symbols) eyes. The bars show the mean phase durations (normalized to each subject's baseline condition, then averaged over subjects) for five contiguous 3-minute sessions (see Figure 3.2.2. for raw data). Immediately after eyepatch removal, phase durations of the deprived-eye pattern increased by 53%, while those of the non-deprived eye decreased by 24%, a two-fold difference between eyes (the effect larger when patching the preferred than the non-preferred eye: factors of 2.6 cf 1.7). The difference in phase duration between the two eyes decayed steadily over time, but remained significant 15 min after eyepatch removal (paired t-test, $n=11$, $\alpha=0.025$, $p<0.01$). Despite the strong bias towards the deprived eye, observers reported that the quality of binocular rivalry did not change after deprivation, with continued alternations between the two monocular images, with almost no periods of fused images.

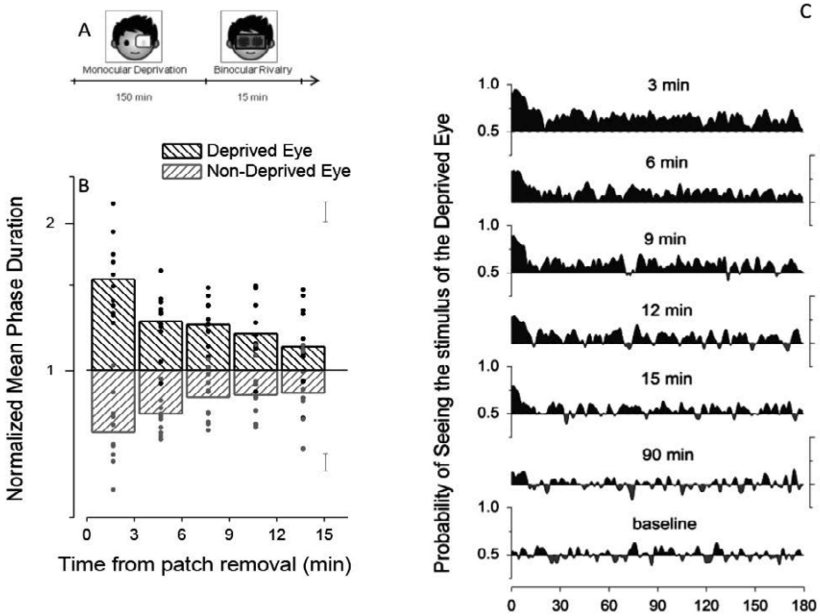

Figure 3.2.1. Effect of monocular deprivation on mean phase durations.
(A) After 150 minutes of patching, five consecutive sessions of Binocular Rivalry were recorded, where observers viewed orthogonally oriented Gabor Patches, vertical to one eye and horizontal to the other. (B) Relative phase durations (expressed as a fraction of the mean baseline phase duration for each observer) of the two visual stimuli, as a function of time elapsed from the removal of the eyepatch, for the stimulus presented to the deprived (black) and non-deprived (light grey) eyes. The points show individual data, the bars group averages: bar symbols at right show average s.e.m.) (C) The average proportion of times observers reported seeing the stimulus presented to the deprived eye, expressed as a function of time elapsed from the onset of each experimental session, smoothed within a Gaussian window of time constant 1 second. For at least 6 minutes after deprivation, the probability stays above chance, indicating that it was always more probable to see the stimulus presented to the deprived eye.

Figure 3.2.1C shows the average instantaneous probability of seeing the deprived-eye stimulus, as a function of elapsed time, averaged over all subjects and sessions and smoothed with a Gaussian window of time constant 1 s. Monocular deprivation biased the trace consistently towards the deprived eye. The initial percept of each testing session (a sensitive parameter of rivalry (Carter & Cavanagh, 2007)) was most strongly biased: in the first session the deprived eye prevailed in 93% of first-phases, remaining at 78% after 15 minutes. Even after 90 minutes, the bias towards the deprived eye remained significant (64%: sign test, $n = 49$, $\alpha = 0.025$, $p<0.001$). After deprivation, gratings viewed by the deprived eye appeared of higher contrast than those by the non-deprived eye, by a factor of 1.36 (on average), but detection thresholds were virtually unaffected. The increase in apparent contrast is qualitatively consistent with the relatively shorter binocular phase periods to the non-deprived eye (Levelt's second law), but the amount of increase is quantitatively insufficient to explain the imbalance in rivalry (see Figure 3.2.3.).

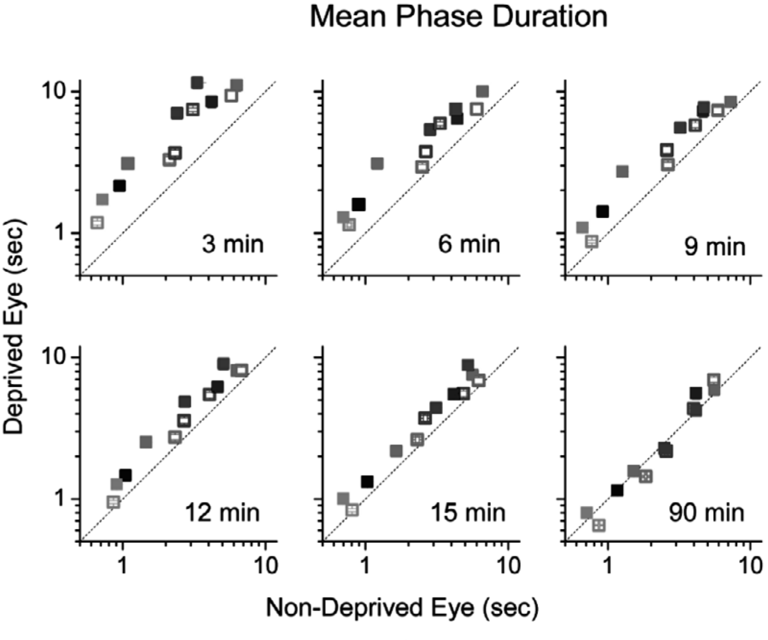

Figure 3.2.2. Raw Dominance Phase Durations after Monocular Deprivation.
For each experimental session, mean dominance phase duration of gratings presented to the deprived eye are plotted against mean phase duration of gratings presented to the nondeprived eye, for various durations after removal of the eyepatch. Different grey levels distinguish the different observers, filled and open symbols refer respectively to preferred and nonpreferred eye patching. For the first 15 minutes after the removal of the eyepatch, all symbols lie upon the bisector of the graph, indicating that mean phase duration of the stimulus presented to the deprived eye was longer than that of stimuli presented to the non deprived eye. 90 minutes after re-exposure to binocular vision, balance between the eyes was restored, with all symbols clustered around the bisector, with a little bias for observers' eye preference. It is well known that mean phase durations during binocular rivalry show a large inter-individual variability(Carter & Pettigrew, 2003): here the range is from 0.7 to 7 seconds.

Within a specific *critical period*, mammalian visual cortex is highly vulnerable to the effects of visual experience: but it is often assumed that mammalian adult visual systems, including humans, show little plasticity after the closure of this period (Berardi, Pizzorusso, & Maffei, 2000). However, there is a growing bulk of literature suggesting that the adult human visual system retains some plasticity (Boroojerdi, Battaglia, Muellbacher, & Cohen, 2001; Karni & Bertini, 1997; Klink, Brascamp, Blake, & van Wezel, 2010; Zhang, Bao, Kwon, He, & Engel, 2009), and some of these alterations, such as perceptual learning, may have long lasting effects. A recent study (Klink, Brascamp, Blake, & van Wezel, 2010) has shown that prolonged periods of binocular rivalry (> 35 min) increases the frequency of mixed or fused binocular rivalry, suggesting that exposure to incongruent signals between the two eyes may decrease the reciprocal interocular inhibition that causes rivalry, promoting fusion rather than competition between the two incompatible images. Our current study complements and expands on that of Klink et al.: 150 minutes of monocular deprivation causes a two-fold prevalence of the deprived eye, with measurable effects lasting up to 90 minutes, revealing a further form of deprivation-induced plasticity in adult human cortex, which boosts signal strength of the deprived eye.

That deprivation causes an increase in apparent contrast suggests that the deprivation-induced changes to the dynamics of binocular rivalry may be mediated by up-regulating contrast gain-control mechanisms in the deprived eye in response to the period of reduced signal-strength. The increase in gain-control probably occurs at the cortical level, given that the patch was translucent (causing no dark-adaption), and the long timecourse of the effects (while retinal and LGN adaptation timecourses are short, Baccus & Meister, 2002). However, the changes were not by themselves sufficient to explain the prevalence of the deprived eye, implicating additional mechanisms specific of binocular rivalry. Gain-control mechanisms are ubiquitous in mammalian brains, and in several neurological dysfunctions, subtle changes of contrast gain have been observed (Dakin, Carlin, & Hemsley, 2005), indicating that the excitatory/inhibitory balance that modulates gain control mechanisms could be particularly susceptible to abnormal developmental events. Increasing cortical contrast gain of the deprived eye may reflect neuroplastic mechanisms attempting to optimize weak or absent information.

Overall, the present results demonstrate that abnormal visual experience can drastically affect adult vision. The effects probably reflect transient changes, not long-lasting as for perceptual learning, in neuronal circuitry in primary visual cortex, possibly related to calibration of the system. That binocular rivalry can reveal significant neural plasticity in adult visual cortex suggests that it could become an important non-invasive tool to assess reorganization of the visual cortex in visual pathologies like amblyopia and to monitor excitation/inhibition balance during plastic changes in human.

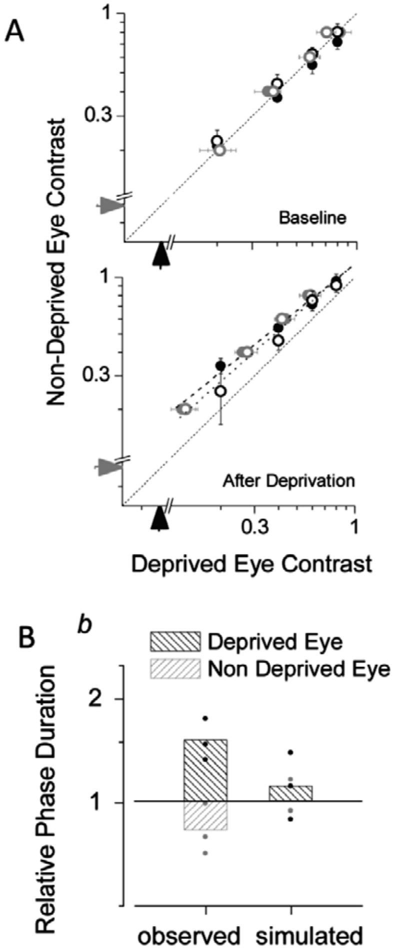

Figure 3.2.3. Effect of monocular deprivation on apparent contrast.
Apparent contrast of stimuli presented after MD for two observers. (A) Observers matched the contrast of a test visual stimulus presented to one eye to that of a "standard" presented to the other eye, in the same spatial location at all contrast tested (0.2, 0.4, 0.6 and 0.8). Before deprivation (upper graph), all points lie on the bisector, showing the precision and accuracy of observer matches. After deprivation (lower graph), stimuli to the deprived-eye (black symbols) need a lower contrast to match the contrast of the non-deprived eye stimuli (light grey symbols), indicating that they appeared of higher contrast. The slope of the linear fit of the data were 0.82 and 0.89 indicating a slight non-linear compression. The black and orange arrows plot the contrast discrimination thresholds, virtually unaffected by. (B) mean phase durations of 3 observers averaged for the first 9 minutes after removal of the eyepatch for stimuli of balanced contrast of 0.75 and for stimuli with unbalanced contrast by a factor of 1.36 (0.9 and 0.66). The phase duration of the low-contrast stimuli is increased by 10%, but clearly insufficient to explain the factor-of-two effect of monocular deprivation.

3.3. Long-term effects of monocular deprivation revealed with binocular rivalry gratings modulated in luminance and in color

The developing sensory brain is highly plastic (Pascual-Leone, Amedi, Fregni, & Merabet, 2005), allowing it to self-calibrate and to adapt to the environment. Plasticity in humans, and indeed all mammals, is regulated within a clearly defined *critical period* (Wiesel & Hubel, 1963b): early visual deprivation, such as early untreated congenital cataracts, provokes permanent deficits both for basic visual functions such as visual acuity and high-level functions such as shape and depth perception (Fine, Smallman, Doyle, & MacLeod, 2002; Fine et al., 2003; Levi, McKee, & Movshon, 2011; Maurer, Lewis, & Mondloch, 2005; Ostrovsky, Andalman, & Sinha, 2006). Plasticity in young infants is so profound that in the congenitally blind, other sensory modalities invade the visual cortex, which starts to respond to tactile (Sadato et al., 1996) and auditory (Roder, Stock, Bien, Neville, & Rosler, 2002) stimulation. Competition between the monocular inputs is a crucial factor contributing to the plasticity of the developing visual system: binocular deprivation affects visual cortex organization of animals less than monocular deprivation (Wiesel & Hubel, 1965a) and humans with unilateral cataracts show more severe deficits than those with bilateral cataracts (Lewis, Maurer, & Brent, 1995).

It has been generally assumed that after closure of the critical period, the brain becomes relatively hard-wired, with little or no experience-dependent plasticity (Berardi, Pizzorusso, & Maffei, 2000; Fine et al., 2003; Hensch, 2004; Maurer, Lewis, & Mondloch, 2005). Recent evidence, however, has questioned this assumption, and the degree of neuroplasticity in adult mammals is now a debated issue. In adult animals, ocular dominance plasticity can be restored by increasing excitation or by decreasing inhibition in the CNS (Harauzov et al., 2010; Maya Vetencourt et al., 2008), confirming the importance of the excitation-inhibition balance in determining visual cortical plasticity. Although in adult humans there is no evidence of ocular dominance plasticity, adult visual cortex shows a residual plastic potential, as demonstrated for fine properties of vision like perceptual learning (Karni & Bertini, 1997), orientation tuning (Bao & Engel, 2012; Zhang, Bao, Kwon, He, & Engel, 2009), contrast discrimination (Kwon, Legge, Fang, Cheong, & He, 2009), multisensory processing (Merabet et al., 2008) and binocular fusion (Klink, Brascamp, Blake, & van Wezel, 2010).

We recently introduced a novel technique to study plasticity in adult humans (Lunghi, Burr, & Morrone, 2011): we combined *binocular rivalry* with *monocular deprivation* – the classic paradigm used to investigate ocular dominance plasticity – to demonstrate that adult human visual cortex retains a surprisingly high degree of neural plasticity. When two incompatible images are displayed separately to the eyes, they do not merge into a single percept, but compete for visual awareness, resulting in ineluctable perceptual alternations with only one image dominating perception at a time, only to be supplanted by the previously suppressed one. This form of bistable perception, called *binocular rivalry* (Blake & Logothetis, 2002), probably reflects reciprocal inhibition of the two rival images (Tong, Meng, & Blake, 2006), making it an optimal tool to study visual competition in early visual processing (Haynes & Rees, 2005). In our previous study we demonstrated that a short period of monocular deprivation

(150 minutes) had important consequences on the dynamics of binocular rivalry between luminance-modulated gratings: following monocular deprivation the deprived eye strongly dominated visual perception over the non-deprived eye, with an effect being measurable for up to 90 minutes following re-exposure to binocular vision.

Here we extend this technique to study the effects of deprivation on binocular rivalry on *equiluminant* chromatic stimuli, modulated in color (to favor the parvocellular system) and compare these effects to those with luminance-modulated grating (reanalyzed from data of Lunghi, Burr, & Morrone, 2011). We show that monocular deprivation affects the dynamics of binocular rivalry for both luminance- and chromatic-modulated stimuli, but more so for chromatic stimuli, where it biases rivalry in favor of the deprived eye for at least 3 hours after 2.5 hours monocular deprivation. Brief periods of deprivation (30 minutes) have very little effect on rivalry.

3.3.1. Materials and Methods

Observers

Five observers (two males, mean age 24±0.8 years), including author CL, participated in experiment with chromatic gratings, and seven observers (one male, mean age 26.7±2 years, all different except CL) participated in the experiment with achromatic gratings. Four participants (one male, mean age 24.5±0.7 years, two who did not participate in other studies) participated in the short-term deprivation experiment. All had normal or corrected to normal vision, normal stereo acuity (Frisby stereotest Sasieni, 1978), normal color vision, and no strong eye preference. Participants gave informed consent and were reimbursed for their time at the rate of 7€ per hour. The experiments were carried out along the principles laid down in the declaration of Helsinki, and the paradigm approved by the ethics committee of the Scientific Institute Stella Maris, and observers gave written informed consent.

Apparatus and Stimuli

The experiment took place in a dark and quiet room. Visual stimuli were generated by the ViSaGe (CRS, Cambridge Research Systems) housed in a PC (Dell) controlled by Matlab programs. Equiluminant chromatic stimuli were displayed on a linearized monitor (Barco CDCT 6551) driven at a resolution of 987x777 pixels, with a refresh rate of 120 Hz. Achromatic stimuli were displayed on a 20-inch Clinton Monoray (Richardson Electronics Ltd., LaFox, IL) monochrome monitor, driven at a resolution of 1024x600 pixels, with a refresh rate of 120 Hz. Observers viewed the display at a distance of 57 cm through CRS Ferro-Magnetic shutter goggles that occluded alternately the two eyes each frame. Responses were recorded through the computer keyboard. The eyepatch was made of a translucent plastic material that allowed light to reach the retina (attenuation 15%), but no pattern information, as assessed by the Fourier transform of a natural world image seen through the eyepatch. During the patching period observers were free to perform their normal activities, such as working, reading, walking outside and having lunch.

Chromatic stimuli were equiluminant sinusoidal gratings, made by summing magenta and cyan sinusoidal gratings of equal but opposite contrast, oriented obliquely at ±45° (size: 2°, spatial frequency: 1.5). They were displayed on a uniform gray background (luminance: 32 cd/m^2, C.I.E: 0.341 0.368) in central vision with a central black fixation point; a common squared dark grey frame (size 2.5°) to facilitate dichoptic fusion. Given that the blue gun was kept constant at 1,the ratio of the red luminance to the sum of the red and green luminance, R/(R+G), was used to determine the subjective equiluminant point of the subjects, evaluated by standard minimum flicker photometry. Points of equiluminance varied between 0.48 and 0.5 for the five observers. To avoid local chromatic adaptation, we randomly shifted the phase of the visual gratings in one or the other direction at a rate of 0.3-0.5 *Hz*. The background was set at the mean value of the individual guns of the equiluminant grating, equiluminance between the gratings and the background was measured with the photometer (Konika Minolta).

Achromatic stimuli were two Gaussian-vignetted sinusoidal gratings (Gabor Patches), oriented either vertically or horizontally (size: $2\sigma = 1.5°$, spatial frequency: 3cpd, contrast: 75%), presented on a uniform background (luminance: 37.4 cd/m^2, C.I.E: 0.442 0.537) in central vision with a central black fixation point and a common squared frame to facilitate dichoptic fusion.

For the equiluminant stimuli, luminance and C.I.E coordinates were 32 cd/m^2, C.I.E: 0.363 0.272 for the magenta grating and 32 cd/m^2, C.I.E: 0.297 0.581 for the cyan grating. Cone contrasts along the axes were LM axis: L=8.5%, M=13.5%; S axis: S=77% (Smith & Pokorny, 1975). The chromaticities of the visual stimuli in a cone excitation space (MacLeod & Boynton, 1979) were: $L/(L+M) = 0.61$ and $S/(L+M)=0.002$ for the red grating and $L /(L+M) = 0.7$ and $S/(L+M)=0.01$ for the green grating. Presentations were alternated at the frequency of the shutter goggles, so each eye was presented with only one of the two stimuli. Monocular deprivation was achieved by having observers wear the translucent eye-patch for 150 minutes for the two main experiments and for 30 minutes in the short-term deprivation experiment.

To test the effect of monocular deprivation on the achromatic and chromatic visual pathway, we used visual stimuli that elicited maximum responses of the two systems: high contrast achromatic Gabor patches with a spatial frequency of 3 cpd and equiluminant magenta/cyan oriented gratings with spatial frequency of 1.5 cpd, because responses to equiluminant sinusoidal gratings show low-pass characteristics (Kaplan, Shapley, & Purpura, 1988). A diagram of the equiluminant visual stimuli is reported in Figure 3.3.1A. The baseline mean phase duration of the two types of visual stimuli was comparable both for the group average (Figure 1B).

Task and Procedure

In the experiment with luminance and chromatic gratings, each observer was measured separately eight times, patching each eye four times in pseudo random order. Each individual patching session was separated at least by 24 hours. We also measured baseline conditions for each observer before patching, yielding eight separate measurements. After patch removal, we measured binocular rivalry continuously for 15 minutes, giving a short break every three minutes. For luminance gratings we measured a three-minute block of rivalry again at 90 minutes from patch removal, for chromatic gratings we measured three-minute blocks at 30, 45, 60 90 120, 150 and 180 minutes. For short deprivation the procedure was the same, but we measured only the first 15 minutes.

Eye dominance was assessed operationally from binocular rivalry baseline recordings, with the dominant eye being the one that prevailed. Immediately after the removal of the eye-patch observers sat in front of the monitor wearing the shuttering goggles and the first experimental session began. After a countdown, the binocular rivalry stimuli appeared. Subjects reported their perception (clockwise or counter-clockwise for the equiluminant gratings and horizontal or vertical for the achromatic gratings) by continuously pressing with the right hand one of two keys (left or right arrows) of the computer keyboard. As assessed in pilot studies and in debriefing sessions, mixed percepts were very rare, occurred for only very brief periods between perceptual transitions, and their frequency remained constant across conditions even after deprivation. Neither subject nor experimenter knew which stimulus was associated with which eye until the end of the session, when it was verified visually.

3.3.2. Results

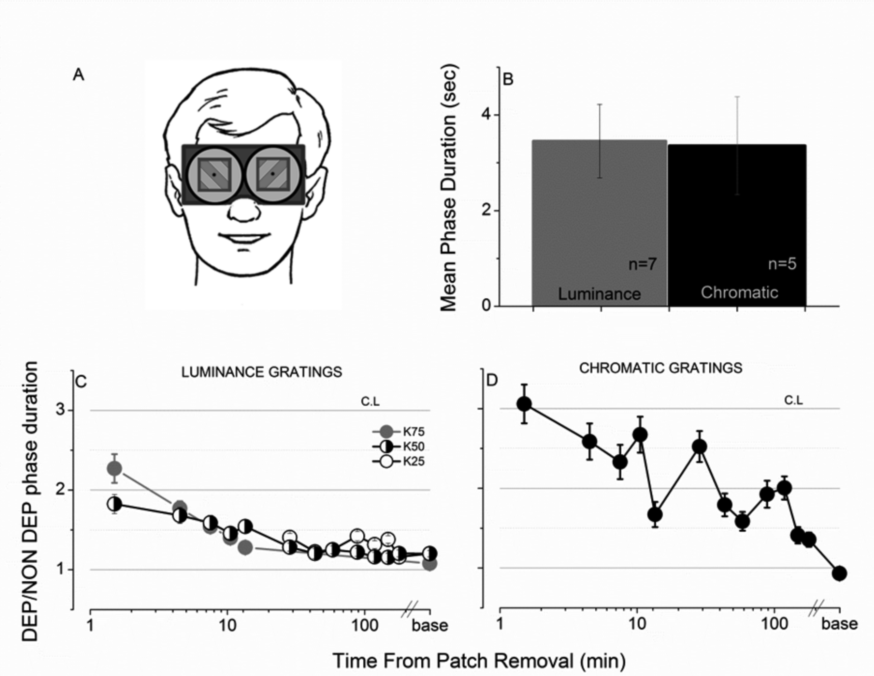

Figure 3.3.1. Mean Phase Durations of the different visual stimuli before and after monocular deprivation. (A) Othogonally oriented equiluminant gratings (S.F. 1.5 cpd, orientation ±45°) modulated only in chromaticity along the L/M axis and achromatic Gabor patches (S.F. 3 cpd, orientation 0-90°) modulated only in luminance contrast (75%) were presented separately to the eyes through FE-Shuttering goggles. (B) Group mean phase durations did not differ for the two visual stimuli tested. (C-D) The average ratio between mean phase duration of stimuli presented to the deprived non-deprived eye of four measurements of a single observer (preferred eyepatched) is plotted as a function of time elapsed from the removal of the eyepatch. (C) When luminance modulated gratings with different contrast (25% - 50% - 75%) were tested, after the first 15 minutes following eye-patch removal, the ratio between deprived eye and non-deprived eye mean phase duration did not statistically differ from baseline measurements. (D) When equiluminant stimuli were tested, the ratio between deprived and non-deprived eye duration significantly differred from the baseline for the whole period tested after monocular deprivation (180 minutes). Error bars represente ±1 s.e.m.

Two groups of subjects wore translucent patches for 150 minutes. After removal of eye-patch, binocular rivalry was tested at regular intervals with luminance- or chromatic-modulated gratings. Data from observers tested with luminance-modulated gratings have been reported briefly (Lunghi, Burr, & Morrone, 2011), and were re-analyzed in this paper to allow a direct comparison with data from the new group of observers tested with chromatic gratings. Fig. 3.3.1 shows the results for one exemplary subject who performed both experiments (author CL). For both luminance- (Fig. 3.3.1C) and color- (Fig. 3.3.1D) modulation, the brief deprivation strongly affected dominance, biasing perception in favor of the deprived eye. The effects were stronger and more long-lasting for the chromatic than for the luminance gratings: on patch removal, binocular rivalry for chromatic gratings was three times more prevalent in the deprived than fellow eye, and the effect lasted for at least 180 minutes. Luminance gratings also biased rivalry towards the deprived eye, initially by a factor of two, lasting for about 30 minutes after patch removal.

As detailed in the methods section, the equiluminant gratings had lower cone contrast than the luminance gratings, 25% compared with 75%. To assess the importance of contrast, we re-measured the effect with luminance-modulated gratings of 50% and 25% contrast. As the results of fig. 3.3.1C show, contrast had very little effect on the bias in rivalry, either in the amplitude or the longevity, effectively ruling out reduced contrast as an explanation for the longevity of the effects with color gratings.

Figure 3.3.2 shows the average results for all subjects (7 for the luminance condition, 5 for color). These average results are similar to those of the example subject of Fig. 3.3.1. For luminance gratings (black symbols), mean phase duration of the deprived eye increased by 56% on eye-patch removal, while that of the non-deprived eye decreased by 28%, a 2.3-fold difference between the eyes. Chromatic gratings (grey symbols) were similar, a 56% increase in the deprived eye, 27% decrease in the non-deprived eye, yielding a factor of 2.3. The baseline measurements do not differ from 1 (implying perfect balance between the eyes). Following 150 minutes of monocular deprivation, the ratio between the deprived and non-deprived eye mean phase duration was significantly (luminance gratings: paired t-test, N=7, t(6)= 6.28, $p \leq 0.001$; chromatic gratings: paired t-test, N=5, t(4)= 4.19, $p \leq 0.05$) biased in favor of the deprived eye (was therefore >1). The effect of monocular deprivation was comparable for the two types of visual stimuli tested during the first 3 minutes following eye-patch removal, but followed different dynamics for luminance and chromatic visual stimuli. When luminance modulated gratings were tested, the effect of monocular deprivation on mean phase durations was only significant for data recorded during the first 15 minutes following re-exposure to binocular vision, data recorded 90 minutes after eye-patch removal clearly show that balance between the eyes was restored (paired t-test, N=7, t(6)= 0.35, p=0.73). For chromatic gratings, rivalry was significantly biased in favour of the deprived eye for at least 3 hours following re-exposure to binocular vision (paired t-test, N=5, t(4)= 2.81 $p \leq 0.05$). 180 minutes after removal of the eye-patch, mean phase duration of the deprived eye was 38% longer than that of the non-deprived eye. In addition, the difference between phase durations for luminance and chromatic-modulated stimuli recorded 12 minutes following re-exposure to binocular vision was statistically significant (t-test, t(10)=2.29, $p \leq 0.05$), a difference that was confirmed also for data recorded 90 minutes after eye-patch removal (t-test, t(10)=2.93, p=0.015). The data are well fitted by a power function of the form:

$$y = 1 + (a/\log(t+1))^b \qquad \text{(eq. 1)}$$

Where *y* is the magnitude of the effect, *t* time expressed in log and *a* and *b* free constants determining respectively amplitude and decay time. The half-life of the effect, defined as the time at which the fitting curve reaches one half the initial effect (value 1.6, indicated by the dashed line in Figure 3.3.2) was 3.7 minutes for luminance-modulated gratings and 27.2 minutes for gratings modulated in chromaticity, showing that the decay of the effect was slower for chromatic stimuli by a factor of 7.3.

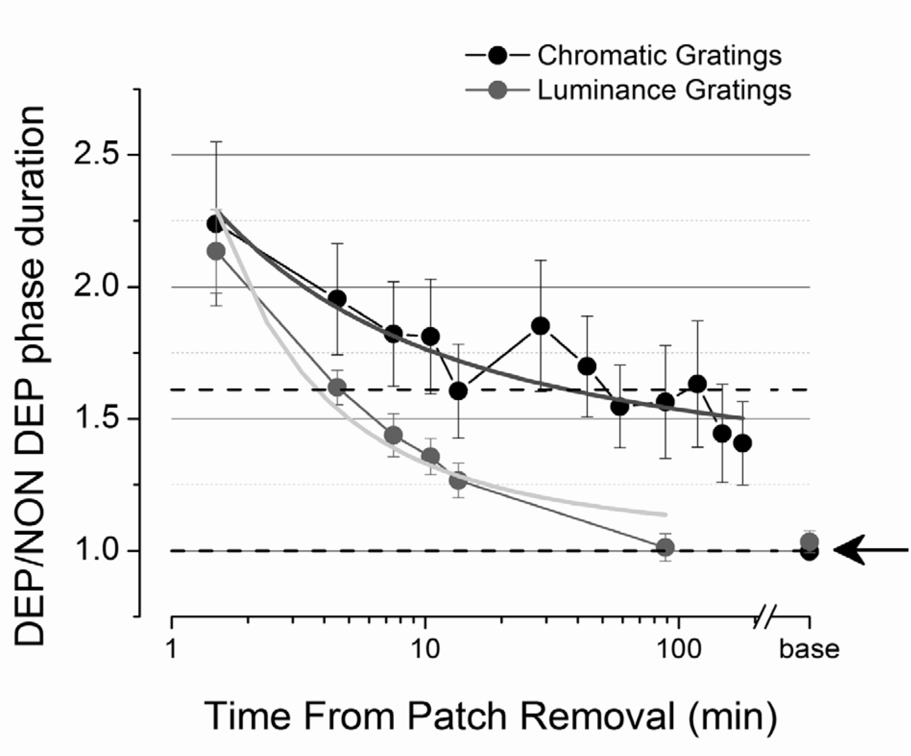

Figure 3.3.2. Effect of Monocular Deprivation on Binocular Rivalry Mean Phase Durations. The ratio between mean duration of the deprived and non-deprived eye is plotted as a function of time elapsed from the removal of the eye-patch for luminance (gray symbols, average of 52 measures, 4 repetitions x 7 observers, only preferred eye was patched for one observer. (Data taken from Lunghi, Burr, & Morrone, 2011) and chromatic (black symbols, average of 40 measures, 4 repetitions x 2 eyes x 5 observers) gratings. Error bars represent ±1 s.e.m. The dashed line represent balance between the two eyes. Following 150 minutes of monocular deprivation phase duration is strongly unbalanced in favour of the deprived eye. The data are well fitted by a function of the form given in eq. 1

To investigate whether shorter periods of monocular deprivation have similar effects on binocular rivalry, we tested a third group of observers with only 30 minutes deprivation, with luminance-modulated gratings. This short amount of deprivation had little effect on rivalry (Figure 3.3.3): during the first 3 minutes, perception was significantly biased towards the deprived eye (paired t-test, N = 4, t(3)=4.72, p≤0.05), but the effect was much less than after 150 minutes of patching, a factor of only 1.26 compared with 2.3. Furthermore, the effect was significant only during the first 3 minutes after patch removal: data recorded later did not differ from baseline measurements.

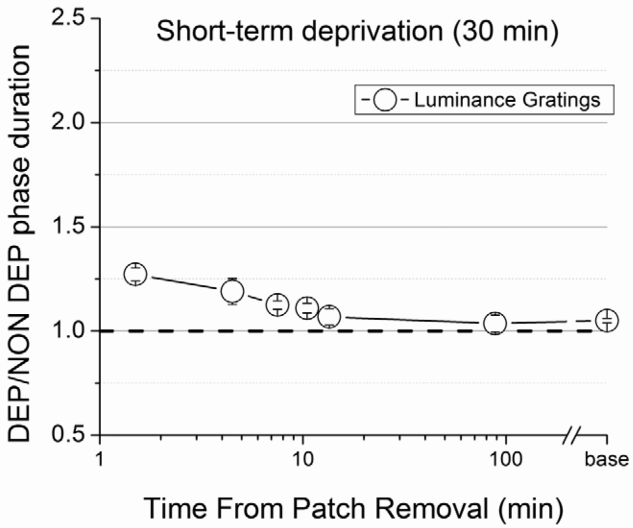

Figure 3.3.3. Effect of Short-Term Monocular Deprivation on Binocular Rivalry Mean Phase Durations.
The ratio between mean phase duration of the deprived and non-deprived eye is plotted as a function of time elapsed from the removal of the eye-patch for luminance-modulated gratings (average of 28 measures, 4 repetitions x 4 observers, only preferred eye was patched for one observer). The dashed line represents equal balance between the two eyes. Following 30 minutes of monocular deprivation phase duration is slightly unbalanced in favour of the deprived eye only during the first 3 minutes following eyepatch removal. Error bars represent ±1 s.e.m.

Rivalry is traditionally characterized by phase-duration distributions, which have a characteristic asymmetrical distribution, usually well approximated by a two-parameter (r, λ) *gamma distribution* of the form:

$$g(x) = (\lambda\^r\, x\^(r-1))/\Gamma(r)\;\; e(-\lambda x) \tag{eq. 2}$$

where Γ is the *gamma function*, r is the shape parameter and λ is the scale parameter (Levelt, 1967). Figure 3.3.4 reports phase-duration distributions of the deprived (black) and non-deprived (orange) eye (normalized for each observer to the baseline mean phase duration of that eye), and the relative gamma-distribution fits, for several 3-minute experimental blocks for luminance (Figure 3.3.4A) and chromatic (Figure 3.3.4B) visual stimuli.

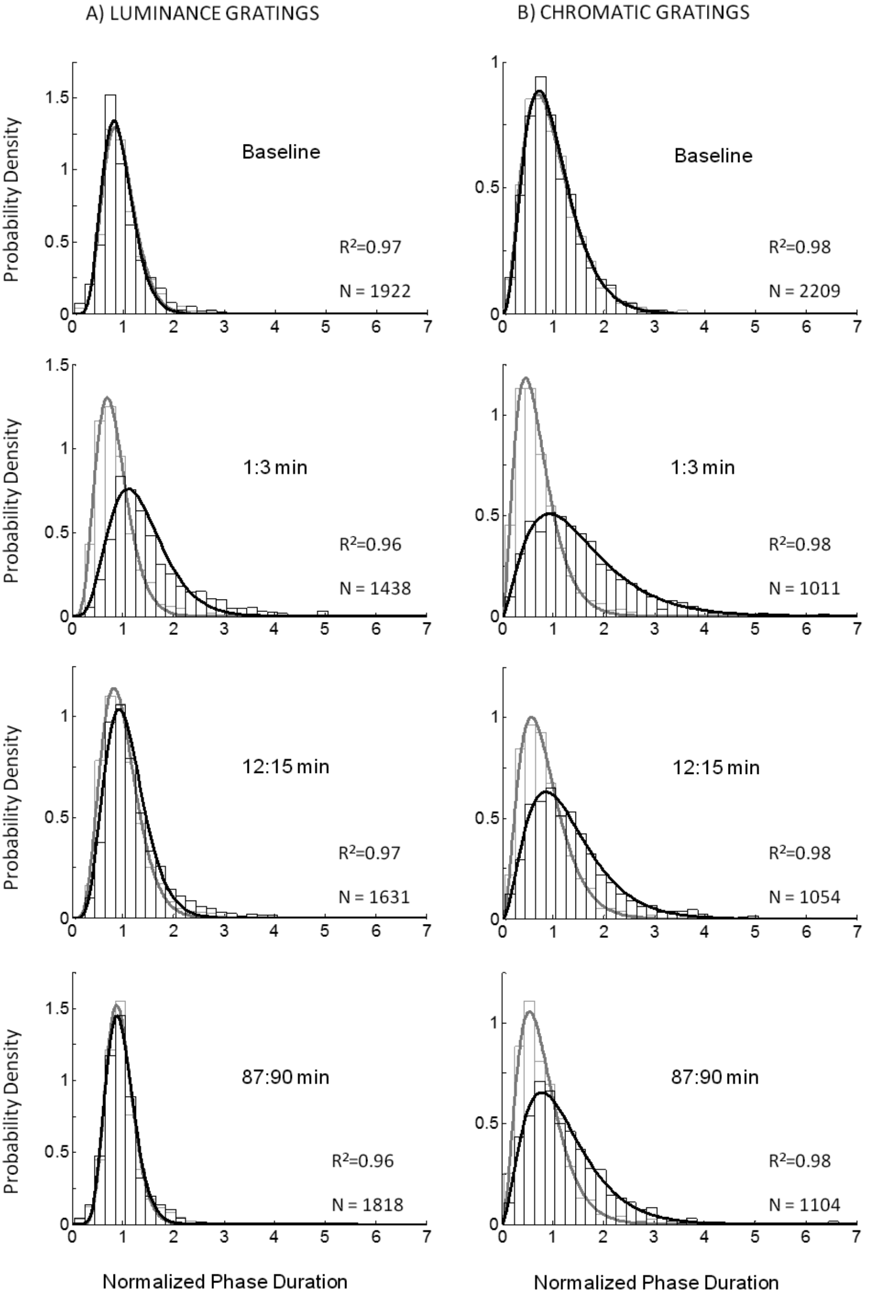

Figure 3.3.4. Phase-duration distributions of the deprived (black) and non-deprived (light grey) eyes, plotted separately for different 3-minutes experimental blocks for luminance (A, data taken from Lunghi, Burr, & Morrone, 2011) and chromatic (B) gratings after monocular deprivation. Phase-durations were normalized to the mean baseline phase-duration for each subject, because of the great inter-individual variability in mean phase duration (from 1 to 9 seconds for luminance gratings, from 2 to 6 seconds for chromatic gratings). Phase durations distributions are well fitted by a two-parameter (λ, r) gamma distribution of the form given in eq.2.

The baseline distributions (top panels) are very similar for the two eyes, with similar values of r and λ. After monocular deprivation, phase-duration distributions of the deprived eye became broader and shifted towards the right (indicating that, on average, all phase durations were longer), while the opposite held for phase duration distributions of the non-deprived eye, indicating that all phase durations were shorter. Nonetheless, the distributions maintained the typical gamma-like characteristics and were well fit by the gamma distribution. The separation between the phase duration distribution of the deprived and that of the non-deprived eye was greater for chromatic than for luminance stimuli: 90 minutes after eye-patch removal, phase-duration distributions of the two eyes were identical for luminance-modulated gratings, while they clearly remained different for chromatic gratings.

Figure 3.3.5 plots the ratio between r and λ separately for the deprived eye (filled symbols) and non-deprived eye (open symbols), as a function of time from eye-patch removal. In line with the literature on the dynamics of binocular rivalry (De Marco, Penengo, & Trabucco, 1977), in the baseline measurements, λ and r of the same eye distribution were virtually identical, approximating unity. Monocular deprivation affected λ and r differently, particularly for chromatic gratings (black symbols): the shape parameter r remained basically unaltered, while the scale parameter λ decreased for the deprived eye and increased for the non-deprived eye. This effect was just as prevalent 120 minutes after removal of eye-patch. For luminance-modulated Gratings (grey symbols), the differential effect on the two parameters was mostly apparent for the deprived eye, while for the non-deprived eye a slight difference between the two was noticeable only during the first 6 minutes of binocular vision.

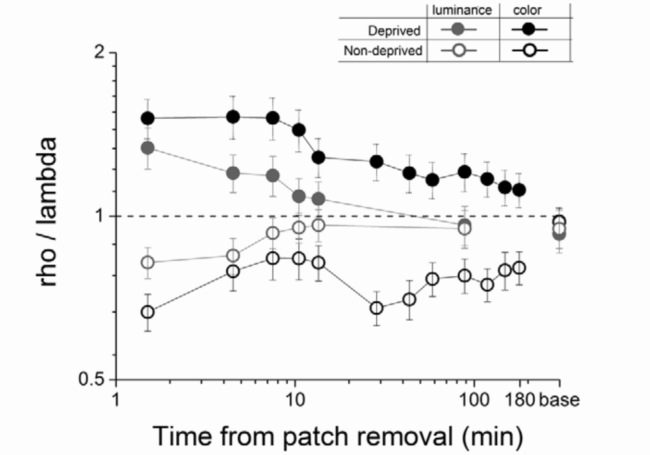

Figure 3.3.5. Phase Duration Distribution Parameters. The ratio between the shape (r) and scale (λ) parameter of the gamma distribution fits (eq. 2), plotted as a function of time elapsed from removal of the eyepatch, for luminance (grey symbols, data taken from Lunghi, Burr, & Morrone, 2011) and chromatic gratings (black symbols) and the deprived (filled symbols) and non-deprived (open symbols) eye respectively. Error bars represent ±1 s.e.m.

The analysis of mean phase durations and phase-duration distributions are standard in binocular rivalry. A more dynamic way of approaching the analysis of bistable perception is to track the probability of perceiving one or other stimulus over time (Lunghi, Burr, & Morrone, 2011; Mamassian & Goutcher, 2005). The advantage of this method is that it describes the dynamics of rivalry, providing a timecourse of visual perception, while the analysis of phase durations does not take into account the order of the events during a period of observation (because of the assumption that phase durations are independently and stochastically distributed). This is important because it has been demonstrated that at least two different processes with different characteristics operate during binocular rivalry, one at the onset of rivalry and one during sustained observation (Carter & Cavanagh, 2007).

We therefore computed the probability of perceiving the visual stimulus presented to the deprived eye (averaged over 6s bins), as a function of time elapsed from rivalry onset, for each 3-minute experimental block. Figure 6 reports the timecourse of the probability of seeing the stimulus presented to the deprived eye for luminance modulated (Figure 3.3.6A) and for chromatic gratings (Figure 3.3.6B). The baseline probabilities oscillate constantly around chance level, indicating that the stimuli presented to each eye were equally likely to be perceived. Monocular deprivation affected both the onset of rivalry and the sustained level of rivalry, but in different ways for luminance and chromatic stimuli. The probabilities recorded after deprivation are well fit by an exponential decay function of the form:

$$y = Ae(t/\tau) + y\_0 \tag{eq. 3}$$

Where y is the magnitude of the effect, A the maximum amplitude, τ the decay constant and y_0 a lower asymptote. After an initial exponential decay, the probability asymptotes to a level (y_0) above chance for all the testing sessions following deprivation when chromatic gratings are tested (Figure 3.3.6B), while for luminance modulated gratings the probability decays to chance level 90 minutes after eye-patch removal and only the bias on onset rivalry is present. When we directly compared the probabilities recorded 90 minutes after re-exposure to binocular rivalry for chromatic and luminance gratings we found that for chromatic gratings the probability of seeing the stimulus presented to the deprived eye was systematically higher than for luminance gratings: taken together both the probabilities recorded during the first 25 seconds of viewing (onset effect) and those recorded during the following 155 seconds (sustained effect) were significantly higher for chromatic gratings (bootstrap sign-test, 1,000,000 repetitions, H_0: chromatic > luminance, $p<0.001$ for the onset effect and $p<0.05$ for the sustained effect).

For luminance gratings, monocular deprivation affected rivalry more at onset than during the sustained period: the asymptotic difference between deprived and non-deprived eye phase durations (i.e. the offset of the decay, y_0) decayed rapidly for luminance gratings to become insignificant 15 minutes after eye-patch removal, while for chromatic gratings the effect remained significant for the whole 3-hour period tested (Figure 3.3.7A). Conversely, the bias in onset rivalry (Figure 3.3.7B), followed a similar timecourse for luminance and for chromatic gratings, even though the onset bias measured 90 minutes following patch removal was higher for chromatic than for luminance gratings (t-test, $t(90) = -2.616$, $p <0.01$). Moreover, for chromatic gratings, the onset bias was significantly higher than chance level after 180 minutes following patch removal (t-test, $t(39)= 2.4655$, $p < 0.02$). Monocular deprivation influences the dynamics of binocular rivalry in different ways, depending on the type of visual stimuli tested, being mostly effective on onset rivalry for achromatic stimuli and effective both on onset and sustained rivalry for chromatic stimuli. This reinforces the suggestion that two processes are at work with binocular rivalry (Carter & Cavanagh, 2007), and these are differently affected in luminance and chromatic gratings after monocular deprivation.

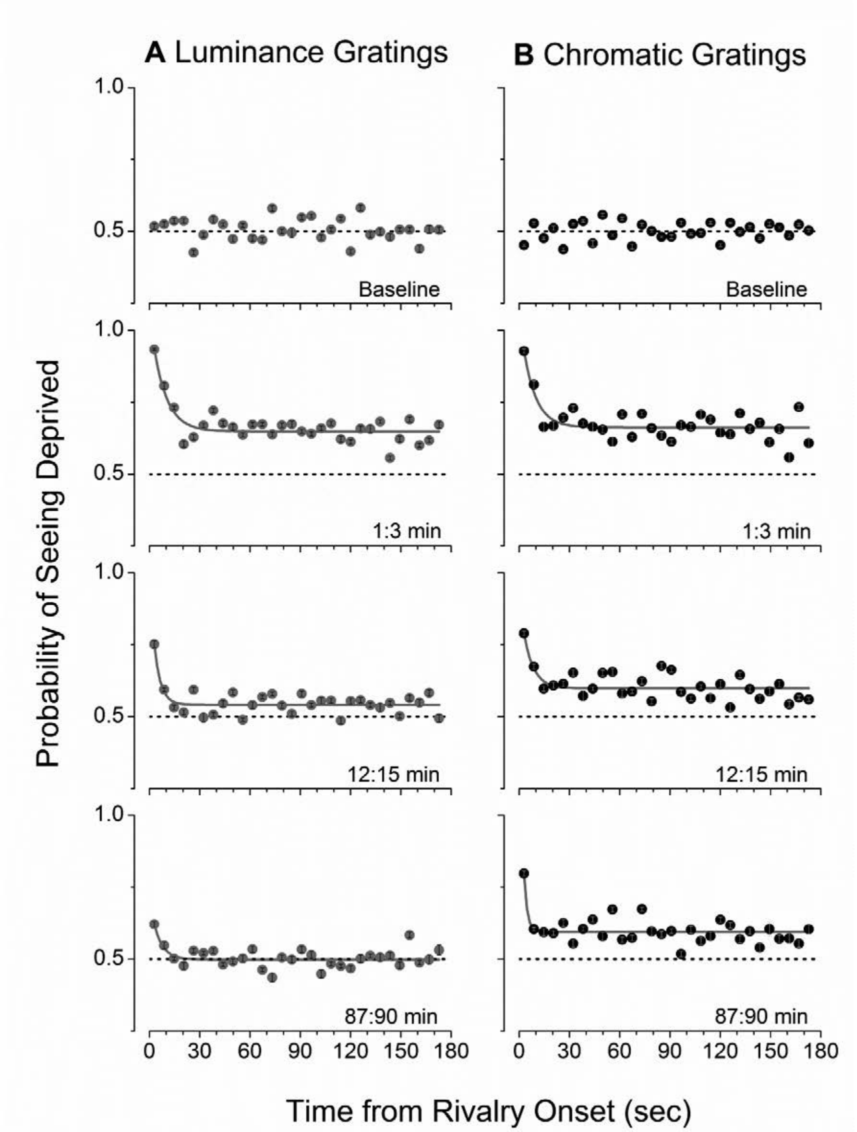

Figure 3.3.6. Average proportion of reported deprived eye dominance.
The probability of perceiving the stimulus presented to the deprived eye expressed as a function of time elapsed from the onset of different 3-min experimental blocks for luminance (A, data taken from Lunghi, Burr, & Morrone, 2011)and chromatic (B) gratings. The probability traces were computed by calculating the frequency of deprived eye dominance (sampling rate = monitor refresh rate, 120 Hz) in 6s bins, for every experimental session recorded (52 for luminance gratings, 40 for chromatic gratings). . The average probabilities across sessions are well fit by an exponential decay function given in eq. 3. Error bars represent 1±s.e.m for every 6 sec bin. The average parameters of the fitting functions are reported in Figure 3.3.7.

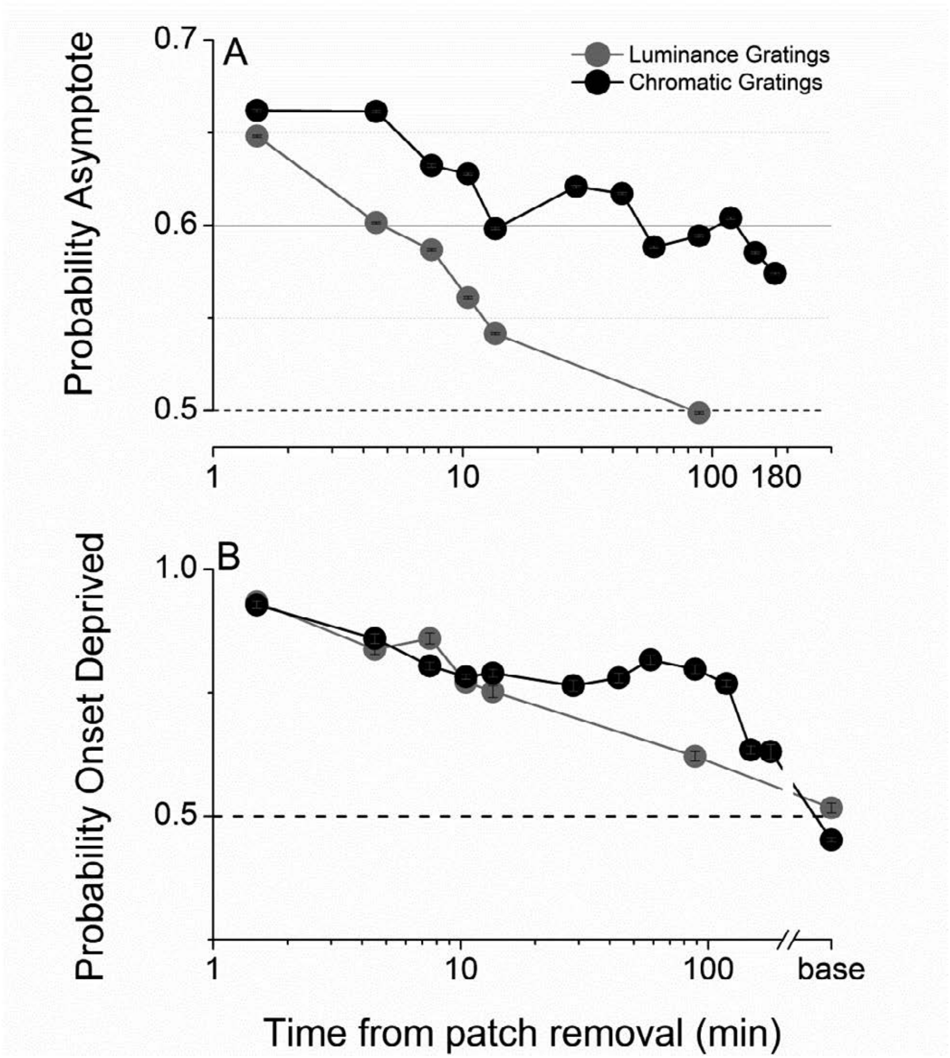

Figure 3.3.7. Probability Trace Asymptote and Onset bias.
A. The asymptote of the effect of deprivation, corresponding to the fitting parameter y_0 of eq. 3, as a function of time elapsed from eye-patch removal. Error bars represent ±1 s.e.m. B. The probability of seeing the stimulus presented to the deprived eye at the onset of rivalry. In both cases gray symbols refer to luminance and black symbols to chromatic gratings. The dashed lines in both graph represent chance level, that is no effect. Error bars represent ±1 s.e.m. (for luminance gratings, data taken from Lunghi, Burr, & Morrone, 2011)

3.3.3. Discussion

Within a specific *critical period* (Hubel & Wiesel, 1970; Wiesel & Hubel, 1963b), the mammalian visual cortex is highly vulnerable to the effects of visual experience, but it is generally assumed that mammalian adult visual systems, including humans, show little plasticity after closure of this period (Berardi, Pizzorusso, & Maffei, 2000; Fine et al., 2003; Hensch, 2004; Maurer, Lewis, & Mondloch, 2005). Our results provide a clear demonstration that the adult human visual system retains a high degree of plasticity, far more than previously thought: two and a half hours of monocular deprivation impacts dramatically on the dynamics of binocular rivalry, causing a two-fold dominance of the deprived eye, with measurable effects lasting up to 180 minutes, depending on the type of visual stimulation. Although the effect could in principle have a sub-cortical origin, we believe this unlikely, given that the patch was translucent (therefore causing no dark-adaption), and that retinal and geniculate alteration of neuronal discharge show a fast adaptation timecourse (Baccus & Meister, 2002; Solomon, Peirce, Dhruv, & Lennie, 2004).

The data reported here point to a plasticity of ocular dominance in adult human visual cortex. Monocular deprivation is an effective technique to reveal plasticity, as it drives competitive Hebbian-like mechanisms, like those responsible for the major neural reorganization within the critical period (Mitchell & Sengpiel, 2009). That following monocular deprivation the deprived eye is reinforced and wins the competition for visual awareness dominating rivalrous perception over the non-deprived eye is an unexpected result, for long-term monocular deprivation usually results in depression of deprived eye input (Wiesel & Hubel, 1963b). Boosting the signal of the deprived eye could be the first response of the visual system to the lack of information provoked by monocular deprivation, an attempt to optimize response to weak stimulation probably by homeostatically modulating contrast-gain mechanisms. Homeostatic bidirectional plasticity has been indeed observed in the mouse visual cortex, where increased responses of both deprived and non-deprived eye have been found after monocular deprivation (Mrsic-Flogel et al., 2007). The importance of competitive mechanisms for visual cortical plasticity as been confirmed by recent evidence (Xu, He, & Ooi, 2010) showing that perceptual learning (where the weak eye is reinforced and contemporarily the strong eye is suppressed) is able to reduce sensory eye dominance and is more effective than a simple reinforcement of the weak eye (Xu, He, & Ooi, 2010).

Some examples of recovery from deprivation have been reported previously, hinting at residual plasticity in human adults. On late removal of unilateral cataracts (Ellemberg, Lewis, Maurer, Brar, & Brent, 2002), some visual recovery was observed, but mainly involving higher cognitive functions such as global motion perception, probably mediated by associative cortex, rather than basic visual sensitivity mediated by primary visual cortex. On the other hand, preserved visual parsing is observed after late removal of bilateral congenital cataracts (Fine, Smallman, Doyle, & MacLeod, 2002; Ostrovsky, Meyers, Ganesh, Mathur, & Sinha, 2009), this is in line with evidence showing that the effects of binocular deprivation (which does not drive neural competition) are less severe and less durable than those of monocular deprivation (Wiesel & Hubel, 1965a).

A few recent experimental studies have shown that short binocular deprivation in adults can reveal some residual neural plasticity in human vision. For example, Kwon, Legge, Fang, Cheong, & He (2009) showed a slight improvement in contrast sensitivity thresholds after four hours of contrast reduction, correlated with an increased BOLD signal in V1 and V2. Boorojerdi et al (2000) observed an increase in excitability of primary visual cortex (TMS phosphene thresholds decreased and BOLD signal in V1 was enhanced) after a few hours of binocular blindfolding, confirming the important role of intracortical inhibition and excitation balance for plasticity (Boroojerdi et al., 2000). This was also supported by results from the same lab demonstrating that benzodiazepine administration completely annuls the effect of light deprivation on cortical excitability (Boroojerdi, Battaglia, Muellbacher, & Cohen, 2001). Zhang, Bao, Kwon, He, & Engel (2009) showed that four hours of selective attenuation of a specific orientation improved slightly discrimination thresholds of the deprived orientation.

In our current study, binocular rivalry, which probes neural, inhibition-generated competitive mechanisms (Blake & Logothetis, 2002; Klink, Brascamp, Blake, & van Wezel, 2010; Levelt, 1966; Tong, Meng, & Blake, 2006), revealed that even ocular dominance, thought to be plastic only during the critical period, has considerable residual plasticity in young human adults. The effect of monocular deprivation that we found on binocular rivalry shares some characteristics with contrast adaptation, such as the exponential decay (Wark, Fairhall, & Rieke, 2009). However, the effects described here are far more long-lasting than those reported for adaptation. Bao & Engel (2012), for example, found that 15 minutes of de-adaptation cancelled the effects of 4 hours of contrast adaptation, whereas our effects persisted for over three hours, longer than the deprivation period, implicating plasticity mechanisms other than those affected by contrast adaptation. The effects may well be related to contrast adaptation, but have characteristics quite different from those reported to date, engaging plastic changes in neural activity that are far more long-lasting than previously described.

Our results show that monocular deprivation had more dramatic consequences on the dynamics of binocular rivalry when chromatic- rather than luminance-modulated gratings were tested. Equiluminant gratings are known to reduce the response of M-cells in favor of P-cells, which are sensitive to chromatic differences (Hubel & Livingstone, 1990; Schiller & Malpeli, 1978). Our results suggest that the parvo-pathway is more susceptible to monocular deprivation in adult humans, as monocular deprivation produced longer-lasting effects, with a slower decay, for chromatic than luminance gratings. These results suggest that the parvo system is affected by monocular deprivation for longer periods compared with the magno system, pointing to a higher degree of plasticity. The hypothesis of a leading role of the parvo system in mediating the effect of Monocular Deprivation on Binocular Rivalry is in line with evidence showing that during the critical period, monocular deprivation has more severe effects on the parvo system, with ocular dominance columns shrinkage of macaque primary visual cortex being larger in layer IVcβ (Horton & Hocking, 1997). Consistent with this evidence, in humans, visual features associated with the magno-system (such as motion perception) are more resistant to visual deprivation, showing spared functions after recovery from blindness (Fine et al., 2003; Maurer, Lewis, & Mondloch, 2005; Ostrovsky, Meyers, Ganesh, Mathur, &

Sinha, 2009), indicating that the parvo system is in general more vulnerable to the effects of visual deprivation.

Different neural functions, even within the same sensory system, may develop at different rates and have different critical periods. There appears to be a link between the developmental time-course of the different visual functions and their vulnerability to abnormal visual experience. The “Detroit Model” of Levi (2005) proposes that visual functions that develop slowly are more sensitive to the effects of sensory deprivation (i.e. retain a higher degree of experience-dependent plasticity), following the principle “last-hired, first-fired” (Levi, 2005). Achromatic and chromatic vision have different developmental timecourses, the first developing fast, the other being a late bloomer in visual development, with VEPs to chromatic stimuli developing much later than those to luminance (Morrone, Burr, & Fiorentini, 1990), and not becoming adult-like until 12-14 years of age in humans, and latencies not completely mature until 17-18 years of age (Crognale, 2002). As chromatic parsing is mostly associated with P-cell activity (Gegenfurtner & Kiper, 2003; Hubel & Livingstone, 1990; Schiller & Malpeli, 1978), the late development of the chromatic vision in humans suggests that P-cells retain a high degree of plasticity even after the closure of the critical period, our results confirmed this spared plasticity.

One interesting point of our results is that monocular deprivation affected rivalry between chromatic and luminance grating in a different way, having more impact on sustained rivalry for equiluminant grating. Onset and sustained rivalry show different characteristics (reviewed in Stanley, Forte, Cavanagh, & Carter, 2012): for example, onset rivalry shows a stable and predictable individual bias that varies across the visual field according to the zones of monocular dominance and is therefore linked to (although not totally explained by) ocular dominance, while a hallmark of sustained rivalry is the unpredictability of the perceptual switches (for accounts on perceptual memory and onset rivalry see also de Jong, Knapen, & van Ee, 2012; Noest, van Ee, Nijs, & van Wezel, 2007; Pastukhov & Braun, 2008). In general, onset rivalry has been shown to be more sensitive to early visual features than sustained rivalry, for example, small imbalances in contrast and luminance between stimuli strongly affect onset rivalry leaving sustained rivalry almost unchanged. Equating the strength of the rivalring images does not annul the stable and consistent bias shown by every observer at the onset of rivalry while balancing stimulus strength equates sustained rivalry dominance (Stanley, Carter, & Forte, 2011). Because of the differences between onset and sustained rivalry, it is likely that the two phenomena are mediated by different mechanisms. The hypothesis of a different contribution of M- and P-pathway to the two types of rivalry, is in line with recent evidence (Denison & Silver, 2012) showing that M-stream is more involved in eye-rivalry, while the P-stream is more engaged in stimulus-rivalry. Stimulus rivalry is a particular form of binocular rivalry revealed by the interocular-switching (IOS) paradigm first proposed by Logothetis, Leopold, & Sheinberg (1996) in which rivalring images are swapped between the eyes 3 times per second and can lead both to rapid-regular switches (eye rivalry) or slow-irregular switches (stimulus rivalry). The finding that monocular deprivation had different effects on binocular rivalry of chromatic and luminance gratings, suggests that onset and sustained rivalry involve different neural mechanisms and possibly a different participation of the Magnocellular and Parvocellular visual pathway. Our results also suggest a different contribution of M- and

P-pathway to the two types of rivalry, the P-pathway playing a major role in mediating sustained rivalry rather onset rivalry.

In our previous brief report (Lunghi, Burr, & Morrone, 2011), we showed that monocular deprivation also influenced apparent contrast, with stimuli presented to the deprived eye appearing on average 36% higher in contrast than stimuli presented to the non-deprived eye. The effect of deprivation on the dynamics of binocular rivalry could not be explained by the boost in apparent contrast because in order to affect mean phase durations in a way similar to deprivation, contrast in one eye had to be higher by a factor of 3. We therefore speculated that short-term monocular deprivation acted by increasing contrast gain of the deprived eye as a first attempt of the visual system to compensate for the lack of information. The fact that monocular deprivation had more severe consequences for equiluminant stimuli could reflect the different contrast gains of M- and P-cells. While M-cells responses rapidly saturate for stimuli above 20% of contrast, most P-cells do not show saturating responses to chromatic stimuli even at high chromatic contrasts (Purpura, Kaplan, & Shapley, 1988; Solomon & Lennie, 2005). If monocular deprivation increases contrast gain of the deprived eye, it is likely to have a greater effect on P-cell responses rather than on M-cells, which are limited by saturation.

The gamma-like shape of phase durations distributions has been considered a hallmark of binocular rivalry and bistable perception in general (Carter & Pettigrew, 2003; van Ee, 2005). However the two parameters defining the gamma distribution usually correlated, and are consequently considered redundant (De Marco, Penengo, & Trabucco, 1977; Mamassian & Goutcher, 2005). One last interesting result from our data is that monocular deprivation disrupted the correlation between the two parameters defining the gamma distribution used to fit phase durations distributions of the two eyes, even though the significance of this finding is uncertain.

3.3.4. Conclusions

In conclusion, we have shown that a brief period of monocular deprivation has drastic consequences on visual perception that are likely to reflect neuroplastic changes at the level of the primary visual cortex. We also showed that the perceptual bias of binocular rivalry showed a much slower decay for chromatic than for luminance gratings, lasting for at least 180 minutes after removal of the eye-patch. As equiluminant gratings are known to reduce response of M-cells, our results suggest that P-cells are more susceptible to the effect of visual deprivation and retain a higher degree of residual experience-dependent plasticity.That the adult visual system retains a high degree of experience-dependent plasticity is important for understanding neural reorganization following late visual loss and for reconsidering sensitive periods in human vision. Binocular rivalry revealed itself as a sensitive probe for neuro-plastic changes and could be a useful non-invasive tool for monitoring plastic changes during occlusion therapy for amblyopia.

3.4. Summary and Conclusions.

We have demonstrated clear functional changes of adult human vision lasting up to 180 minutes after brief periods of deprivation of pattern vision to one eye. Following 180 minutes of monocular deprivation of pattern vision changed dramatically the dynamics of binocular rivalry, causing the *deprived eye to dominate* conscious perception over the non-deprived eye in adult humans. This paradoxical result indicates that the visual system initially reacts to monocular deprivation by homeostatically boosting activity of the deprived eye in order to compensate for the lack of information caused by deprivation.

We propose that the neural changes underlying this form of monocular-deprivation-driven neuroplasticity is an up-regulation of contrast gain control mechanisms, hypothesis that is supported by the evidence that after monocular deprivation images presented to the deprived eye appeared to be higher in contrast compared to images presented to the non-deprived eye.

We have also shown that the effects of monocular deprivation are more long-lasting (the duration of the effects increases by a factor of 2) when equiluminant gratings are tested compared to luminance-modulated gratings. This result suggests a higher vulnerability of chromatic vision to the effect of monocular deprivation and possibly a higher degree of residual plasticity for the Parvocellular pathway.

Taken together, these results call for a re-evaluation of adult visual cortical plasticity, fundamental to understanding how the adult visual system reacts to sensory loss, with implications for developing therapeutic strategies that exploit the intrinsic plasticity of the visual cortex.

Chapter 4
Binocular Rivalry as a tool to monitor visual system plasticity during occlusion therapy in amblyopic children

4.1. Introduction

We have demonstrated that the adult human visual system retains a degree of neuroplasticity higher than previously thought: 150 minutes of monocular deprivation using a translucent eyepatch had important perceptual consequences, favouring dominance of the deprived eye during binocular rivalry (Lunghi, Burr, & Morrone, 2011), with a significant effect being measurable up to 180 minutes following eyepatch removal, depending on the type of visual stimuli used.

Plasticity is a fundamental property of the developing visual brain, allowing dynamic adaptation of the young organism to the environment. Taking advantage of the incredible plastic potential of young children's visual system, the most classic treatment for amblyopia (that is the most common cause of visual impairment in children) is *occlusion therapy*, consisting in patching the fellow eye in order to force the brain to use the weaker amblyopic eye reinforcing its connections.

Having demonstrated that binocular rivalry is a sensitive probe for visual plasticity following monocular occlusion, we were interested in investigating the perceptual consequences of prolonged monocular deprivation on rivalry dynamics, we therefore tested binocular rivalry during occlusion therapy (that requires patching of the fellow eye over extended periods of time) in amblyopic children. Data recorded so far are still preliminary, but they are encouraging, suggesting that binocular rivalry can be used to monitor visual plasticity during occlusion therapy.

4.1.1. Amblyopia

Amblyopia is defined as a developmental disorder of spatial vision in which a deficit in visual acuity is present despite an apparently physically normal eye, a deficit that is not optically correctable and is commonly known as "lazy eye" syndrome. Amblyopia is usually associated with strabismus, anisometropia and early visual deprivation (i.e. early onset or congenital cataracts), Ciuffreda, Levi, & Selenow, 1991; Levi & Li, 2009, and is one of the most frequent causes of visual loss in infants and young children, affecting 1-5% of the human population (Webber & Wood, 2005). Amblyopia severity correlates with the onset age of the disease, that appears to have a "sensitive period" spanning from the first year of life to 6-8 years of age in humans (D. H. Baker, Meese, & Hess, 2008; Maurer, Lewis, Brent, & Levin, 1999; Maurer, Lewis, & Mondloch, 2005). The onset of the sensitive period for amblyopia

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seems to be strictly associated with the development of binocular interactions in primary visual cortex and with the development of visual sensitivity to high spatial frequencies that are more susceptible to the blur caused either by high refractive errors or by cataracts (Kiorpes, Kiper, O'Keefe, Cavanaugh, & Movshon, 1998); the end of the sensitive period for amblyopia correlates with the end of the critical period for the same features.

The severity of the visual loss associated with amblyopia increases with increasing imbalance between the eyes (anisometropia) rather than for binocularly equivalent refractive errors (isometropia) because of the competitive interactions between the eyes in establishing and reinforcing the neural connections with the visual cortex (McKee, Levi, & Movshon, 2003; Weakley, 2001). Isoametropic refractive patients in fact do not develop amblyopia and show much less severe pattern of visual loss and spared stereoacuity compared to anisometropes (Levi, McKee, & Movshon, 2011). Binocular blur appears therefore to be more tolerated by the visual system than monocular blur; if not treated early after birth, in fact, monocular cataracts provoke severe amblyopia (for review see (Maurer, Lewis, & Mondloch, 2005).

One of the important factors in determining the pattern of visual loss associated with amblyopia is binocularity, which is totally devastated in strabismic amblyopes. Anisometropic patients lacking of binocular function in fact show patterns of visual deficits similar to those of strabismic patients. Deficits in contrast sensitivity, spatial resolution (acuity) and stereoacuity associated with anisometropia have been thoroughly investigated by Levi, McKee and Movshon (Levi, McKee, & Movshon, 2011). They demonstrated that acuity is impaired with increasing anisometropia, with strabismus having a multiplicative effect (factor of 2.5) on spatial acuity, while contrast sensitivity has been shown to be less sensitive to anisometropia severity, that is (as anticipated above) instead crucial for stereopsis. In general, anisometropes lacking of binocularity show severe amblyopia and a longer prognosis with treatment (Kivlin & Flynn, 1981).

4.1.2. Occlusion Therapy

The most common and traditional treatment for amblyopia is the occlusion therapy, that consists in patching the fellow eye for an amount of hours per day ranging from 2 hours to full time depending on the severity of the disease (i.e. the degree of anisometropia). The idea behind the occlusion therapy is to force the patient to use the “lazy eye”, obliging the brain to use the weaker connections from the amblyopic eye with the aim of reinforcing them. The success of the treatment depends on the patching dose, on whether or not the patient shows spared binocular function, on the presence of strabismus, the severity of amblyopia and the age of the patient (Stewart, Moseley, Stephens, & Fielder, 2004). The dose-response of the occlusion therapy shows a long time constant, with acuity of the amblyopic eye improving of about 26% for every 120 hours of treatment and requires therefore patching over extended periods of time (from a few months up to one year or more).

Since sensitivity to high spatial frequency is a crucial factor for the development of amblyopia, during the past decade a less aggressive form of occlusion has been proposed for the treatment of amblyopia that consists in applying Bartenger foils on the spectacle lens of the fellow eye rather than using an opaque eyepatch (a too aggressive patching could be in fact detrimental provoking a visual loss of the fellow eye). Bartenger foils (Ryser Optik, Gallen, Switzerland) are translucent diffuser filters made of scattering micro-elements designated to reduce visual acuity by different levels, depending on the strength of the filter. Bartenger foils act by attenuating the high and mid-range of spatial frequencies without showing spurious resolution and phase shifts (Perez, Archer, & Artal, 2010), and have been demonstrated to be effective for the treatment of moderate amblyopia (Iacobucci, Archer, Furr, Martonyi, & Del Monte, 2001).

Even though occlusion therapy is thought to be maximally effective if administered during the sensitive period for amblyopia (so within the first 6-8 years of age) there is some evidence showing residual plasticity of the amblyopic visual system of older children and young adults, even though a more aggressive treatment is required to obtain some improvement in young adults (Kupfer, 1957). More evidence in favour of a residual plastic potential of the adult amblyopic visual system is obtained from studies showing an improvement of the amblyopic eye acuity following a visual loss of the fellow eye (macular degeneration, El Mallah, Chakravarthy, & Hart, 2000, refractive errors, Rahi et al., 2002). The loss of acuity in the fellow eye is thought to unmask the connections from the amblyopic eye that are likely to be suppressed and not destroyed.

4.2. Binocular Rivalry during occlusion therapy

We have previously demonstrated that following a brief period of monocular deprivation (150 minutes), visual perception of adults during binocular rivalry is strongly biased in favour of the deprived eye that wins the struggle for visual awareness over the non-deprived eye (Lunghi, Burr, & Morrone, 2011). Our results are apparently in contrast with the outcome of occlusion therapy used to treat amblyopia, because we showed, counter intuitively, a strengthening of the deprived eye following monocular patching. However, binocular rivalry is a peculiar phenomenon, whose dynamics are not necessarily linked with the mechanisms underlying neural plasticity mediating the recovery of visual acuity of the amblyopic eye observed during the occlusion therapy. It is therefore interesting to test binocular rivalry during the occlusion therapy in amblyopic patients in order to investigate the relationship between the perceptual bias observed in adults after monocular deprivation with the recovery of amblyopia during monocular deprivation of the fellow eye.

Another difference between our study and occlusion therapy is the duration of monocular deprivation: we were in fact only able to test short-term deprivation (150 minutes) and we cannot exclude therefore the involvement of different neural mechanisms after prolonged patching. During occlusion therapy, patients are required to wear the Bartenger filter for an extended period of time (several months), allowing to test the effect of monocular occlusion on the dynamics of binocular rivalry after prolonged eye-patching, that would be otherwise impossible with normal observers.

4.2.1. Materials and Methods

Subjects

Five children (one female), mean age 5.8±0.42, participated in the experiment. Children aged between 5 and 7 years were selected because of the developmental timecourse of binocular rivalry (Hudak et al., 2011; Kovacs & Eisenberg, 2005). All of them were anisometropic amblyopes at the first examination after the prescription of the spectacles. All had spared binocularity (Lang test) and didn't show strabismus. None of them had been previously treated with occlusion therapy. The experiment was performed according to the principles of the Declaration of Helsinki and was approved by the ethics committee of the hospital (Azienda Ospedaliaro-Universitaria Meyer, Florence). Children were accompanied by their parents, who were also present during the test. Written informed consent was obtained from the participants' parents.

Apparatus and Stimuli

The experiment was set up in the outpatients' ophthalmology department at the hospital Meyer in Florence. The room was dark and quiet. Participants were first tested for visual acuity (Snellen acuity) of their two eyes using vector Snellen Charts for children. Table 3.4.1 reports children's visual acuity measured at different time intervals from the beginning of the occlusion therapy.

Visual stimuli were generated by a portable VSG 2/5 (CRS, Cambridge Research Systems) housed on a laptop (DELL) and controlled by Matlab programs, they were displayed on a gamma-corrected CRT monitor (MODEL) driven at a resolution of 1024X600 pixels, with a refresh rate of 120 Hz. Observers' head was stabilized with a chinrest placed at a distance of 57 centimeters from the monitor, participants viewed the visual stimuli through CRS FE-Shuttering Goggles that were fastened to the chinrest. The goggles were synchronized with the monitor refresh rate through the VSG 2/5 and occluded alternatively the two lenses at each frame allowing dichoptic viewing.

Visual stimuli were achromatic orthogonal (horizontal and vertical) Gabor patches (size 2°, spatial frequency 2 cpd, contrast 75%) presented on a uniform average grey background (luminance 37 cd/m^2) in central vision, with a black fixation point and a black common squared frame (size 2.5°). Observers reported verbally their visual perception and responses were recorded through the computer keyboard manipulated by the experimenter.

Occlusion therapy was achieved by sticking a Bartenger 0.4 filter on the spectacle lens of the fellow eye. Since the optical features of the Bartenger foils are not homogeneous and often differ from the labeled density designation (Perez, Archer, & Artal, 2010), each filter was first controlled by the experimenter for the correct level of blur by measuring Snellen acuity through it and was then applied on the appropriate spectacle lens.

Task and Procedures

To make the setup and the task appealing for children, we covered the monitor with a black cloth with yellow stars pinned on it and we stuck some cartoon characters on the monitor in order to make it look like a sort of "magic box". A picture of the setup is reported in Figure 4.1. We invented a story, that we told to the children showing a Power Point presentation, about a magic competition and we asked the children to be the referees of the context, telling them that the magic tricks could only be seen through the goggles. Children were very keen to perform the task, some of them even enthusiastic. They were trained to report verbally whether the "stripes" (Gabor patches) on the monitor were "standing up" (vertical) or "lying down" (horizontal). The experimenter held the appropriate key of the computer keyboard according to the visual perception reported by the observer. Children were motivated to perform accurately the task because at the end of each 3-minutes experimental block they were asked to judge which of the characters had won the magic context (one was associated with the horizontal, the other with the vertical orientation). The orientation presented to each eye was swapped at every session as well as the orientation associated with a particular character, in order to reduce the possibility of response bias in favour of one or the other orientation.

During the first training session binocular rivalry was simulated by presenting the same orientation to both eyes and changing it at random intervals mimicking the dynamics of binocular rivalry. During the training session the experimenter could check the accuracy of the child and ended the trial when the observer reported the visual orientation precisely. Children that were not able to perform the task were discarded and did not take part to the binocular rivalry experiment.

After the training session a short (90 seconds) binocular rivalry session was recorded to determine the quality of binocular rivalry for the different children. Observers that did not show binocular rivalry (either not alternating at all or fusing the two visual images reporting to perceive a plaid) were discarded. None of the observers that we considered for analysis reported periods of patchy rivalry. Binocular rivalry was measured before the placement of the Bartenger foil on the lens of the fellow eye (baseline measurements) and at different time intervals following the onset of the occlusion therapy: 120 minutes, 30 days, 60 days, 150 days. 2x180 seconds experimental blocks were recorded for each interval.

Figure 4.1. Experimental Setup
Two pictures of the child-friendly experimental setup are shown. The child sat in front of the monitor, the head was stabilized by a chin and forehead rest and the shuttering goggles were attached to it. The monitor was covered with a black cloth and yellow stars and a "sorcer Mickey Mouse" cartoon was stuck in correspondence of the visual stimulus. Children were asked to help Mickey Mouse in judging the magic context and were told that the goggles were especially constructed to show magic tricks.

4.2.2. Preliminary results

The outcome of the occlusion therapy is shown in Table 4.1, where visual acuity of the two eyes is reported for the different time intervals tested. All children showed an improvement of visual acuity of the amblyopic eye, improvement that, for some children, was virtually complete two months after the beginning of the treatment and stabilized 5 months after. If binocular rivalry dynamics were governed by the same neural mechanisms underlying the recovery of amblyopia we would expect to observe an initially strong perceptual bias in favour of the fellow eye (that we will define as the *deprived eye* because it is the one that will undergo the patching procedure) and a subsequent reduction of the bias, with balance between the eyes being restored with recovered acuity of the amblyopic (*non-deprived*) eye.

Subject	**Date of Birth**	**Initial Visus**	**Visus after 1 month**	**Visus 2 months**	**Visus after 5 months**
S1	18-08-06	RE 0.9 – LE 0.6	-----------------	RE 0.9 – LE 0.9	RE 1.0 – LE 1.0
S3	26-02-05	RE 0.4 – LE 1.0	-----------------	RE 0.7 – LE 1.0	RE 0.8 – LE 1.0
S6	12-06-06	RE 1.0 – LE 0.5	RE 1.0 – LE 0.7	RE 1.0 – LE 0.9	-----------------
S7	12-07-05	RE 1.0 – LE 0.4	RE 1.0 – LE 0.8	RE 1.1 – LE 0.9	-----------------
S8	06-04-04	RE 1.0 – LE 0.6	RE 1.0 – LE 0.7	RE 1.0 – LE 0.8	-----------------

Table 4.1. Participants' age and visual acuity in the two eyes.
The table reports the date of births of the five children tested and the visual acuity of the right and left eyes (RE and LE) measured using Snellen tables. All children show an improvement of visual acuity of the amblyopic eye following occlusion therapy. The improvement is already important 1 month after the onset of the treatment.

The proportion of time spent by the observers seeing the stimulus presented to the deprived (fellow) eye for the different time intervals recorded is reported in Figure 4.2. The dashed line represents perfect balance between the two eyes (with dominance proportion being 50%). In the baseline measurements, surprisingly, all but one observer showed balanced rivalrous perception, despite anisometropia. We chose visual stimuli having an optimal spatial frequency (2 cycles per degree of visual angle), that should be well visible even for the amblyopic eye, the blur caused by amblyopia, in fact, principally affects high spatial frequencies. Nevertheless, this result indicates that the dynamics of binocular rivalry are not affected by the weakening of the signal from the amblyopic eye provoked by the pathology, suggesting that binocular rivalry engages different neural mechanisms.

Equally surprising is the result that the occlusion of the fellow eye disrupted the initial balance, with visual perception during binocular rivalry being biased in favour of the deprived (fellow) eye. The measurements recorded 2 hours after the onset of the occlusion therapy confirm our previous findings obtained with adult normal observers undergoing monocular patching (Lunghi, Burr, & Morrone, 2011). Interestingly, the bias in favour of the fellow (deprived) eye is maximum 30 days following the onset of the treatment, with the deprived eye dominating competition with the non-deprived (amblyopic) eye 80% of the time, despite the recovered acuity of the amblyopic eye compared to the baseline measurements. 60 days after eye-patching, the recovery of the amblyopic eye is almost complete and balance between the two eyes during binocular rivalry is restored, balance that is confirmed in measurements recorded 150 days after the onset of occlusion therapy.

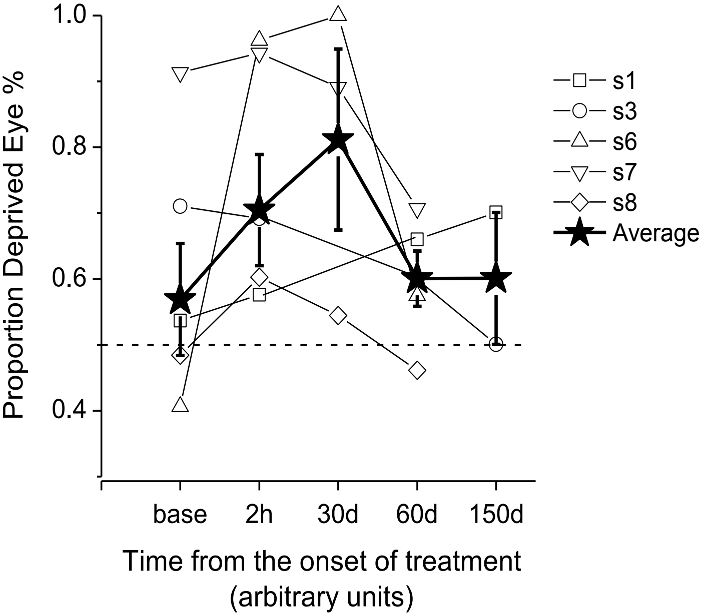

Figure 4.2. Proportion of Dominance in favour of the deprived eye.
The proportion of time spent seeing the visual stimulus presented to the deprived (fellow) eye is plotted as a function of time elapsed from the onset of the occlusion therapy (temporal units on the x scale are arbitrary). The dashed line represents perfect balance between the eyes. The small hollow symbols stand for individual observers' performance, while the full black stars are the average (error bars represent s.e.m). Despite anisometropia, the baseline measurements show a balanced visual perception during binocular rivalry. Following monocular patching with Bartenger 0.4 filters, visual perception is biased in favour of the deprived eye, the bias is already present 2 hours following patching and is maximum 30 days after. 60 days following the beginning of treatment, balance between the eyes is re-established and reinforced 150 days after, when the amblyopic eye has virtually completely recovered (see Table 3.4.1).

4.2.3. Discussion

The data presented above are still preliminary and incomplete, and much more work needs to be done, but nevertheless, they show an interesting trend: the dynamics of binocular rivalry recorded before and during occlusion therapy seem to be unrelated with the visual loss provoked by amblyopia and the subsequent recovery of visual acuity during the treatment. Before the onset of the therapy, in fact, all observers tested had an important anisometropia between the eyes, with visual acuity being perfect in the fellow eye and impaired in the amblyopic eye. Nevertheless, surprisingly, observers' perception during binocular rivalry was balanced, with only one child showing a strong perceptual bias in favour of the fellow eye.

During occlusion therapy visual acuity of the amblyopic eye improved and was virtually recovered two months following the beginning of the treatment. Interestingly, during the first month of treatment, that is when plasticity is maximum and the amblyopic eye rapidly improves visual acuity, the initial perceptual balance between the eyes was disrupted and visual perception during binocular rivalry was strongly biased in favour of the fellow (deprived) eye, that dominated 80% of the time over the amblyopic (non-deprived) eye. The initial perceptual balance between the eyes was then re-established two months following the onset of the treatment and reconfirmed five months after, when visual acuity of the amblyopic eye was stabilized and neural-plasticity probably lowered.

The marked dissociation between the strength of the visual signals (diminished by amblyopia and then recovered during the treatment) and visual perception during binocular rivalry suggests that different neural mechanisms underlie the two phenomena. Binocular rivalry is a peculiar case of bistable vision that engages competition between the monocular inputs and the neural representation of the rivalring visual stimuli at different stages of neural processing (for review see: Tong, Meng, & Blake, 2006). Importantly, binocular rivalry also engages strong adaptation and reciprocal inhibition between the eyes (for review see: Alais, 2012) and is in principle sensitive to the level of intracortical inhibition of the visual cortex.

Balance between intracortical inhibition and excitation at the level of the visual cortex is crucial for experience-dependent plasticity. As discussed in the introduction (3.1), the development of GABA-ergic inhibition is one of the most relevant factors provoking the closure of the critical period in mammals (Fagiolini & Hensch, 2000), and plasticity in adult animals can be restored by decreasing pharmacologically the levels of intracortical inhibition (Harauzov et al., 2010; Maya Vetencourt et al., 2008). Finally, GABA-ergic neurons are the only cells in the visual cortex retaining some form of experience-dependent plasticity (Hendry & Jones, 1986; Lee et al., 2006). If experience-dependent plasticity driven by the occlusion therapy causes some changes in intracortical inhibition (probably lowering the level of GABA-ergic inhibition), the perceptual changes observed in binocular rivalry are likely to reflect the timecourse of neural plasticity during the treatment of amblyopia.

Even though our data are still preliminary and the interpretation speculative so far, the correlation between visual acuity recovery and the perceptual bias in favour of the fellow eye that we observed is striking and suggests that binocular rivalry could be an useful non-invasive tool to monitor the efficiency and timecourse of occlusion therapy for amblyopia and maybe predict its outcome.

Chapter 5
General Conclusions

In this work we have revealed some unexpected properties of the early visual cortex. We have challenged the view that considers primary sensory areas as being exclusively dedicated to unisensory processing by showing that touch can interact with vision during binocular rivalry at early stages of visual analysis, probably already in V1. Our results have further challenged the notion of neuroplasticity being restricted to a sensitive period early in life by demonstrating that a brief period of monocular deprivation in adult observers provokes important perceptual effects that results in unbalancing visual perception during binocular rivalry in favour of the deprived eye with an effect being measurable for a period of time exceeding the duration of deprivation.

We propose that using binocular rivalry as psychophysical method to investigate these aspects of visual perception is the crucial factor that allowed the discovery of these important properties of early visual cortices. Binocular rivalry, in fact is a peculiar visual phenomenon presenting unique characteristics that can be used to unmask subtle behavioural effects. For example, the intrinsic ambiguity of visual rivalrous perception can help in unmasking signals from other sensory modalities, that are normally concealed by a strong and reliable visual input, without needing to weaken visual stimulation by degrading the visual stimuli. In addition, since binocular rivalry requires the interaction between monocular signals, it is resolved at the cortical level, that is the first stage of neural processing in which the monocular signals are integrated. Using binocular rivalry therefore ensures that the cortical origin of the neural processes that are investigated.

One of the most stryking features of binocular rivalry is the dissociation between constant physical stimulation and alternating visual perception: albeit two different visual stimuli are contemporaneously displayed on the retinae, only one of them is consciously perceived at a time, the other being suppressed from visual awareness. While the neural signal associated with the dominant visual stimulus is processed by a complex hierarchy of cerebral areas, starting from primary visual cortex and reaching object-sensitive areas in the infero-temporal cortex, the neural trace of the suppressed visual stimulus is not treacable outside of V1 or V2. Factors interfering with the suppressed visual signals are therefore extremely likely to reflect neural interactions occurring at these early stages of visual processing. This aspect of binocular rivalry importantly revealed the early interaction between vision and touch that we found.

Binocular rivalry engages strong competition between the monocular signals and is therefore a sensitive probe for measuring the relative strength of the signal associated with each eye. Other psychophysical methods, in fact, involve collaborative

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rather than competitive interactions between the eyes. Binocular rivalry is a unique method to separately track the strength of the monocular signals in a context in which they compete with each other. This is the property of binocular rivalry that was crucial for revealing the effects of monocular deprivation on adult visual perception, for competition between the monocular signals is one of the important factors underlying neuroplastic changes in the visual cortex.

Moreover, visual competition during binocular rivalry is thought to be driven by reciprocal inhibition between the monocular signals. Binocular rivalry could therefore be used as a sensitive method for indirectly evaluate the balance between intracortical inhibition and excitation, the dynamics of binocular rivalry being regulated by inhibitory processes. Balance between inhibition and excitation at the cortical level is crucial for neuroplasticity, for either increasing excitation or decreasing intracortical inhibition restores neuroplasticity in the visual cortex of adult animals and critical periods depends on the development and maturation of GABAergic inhibition. This characteristic is probably the reason why we have shown that binocular rivalry can be efficiently used as a non-invasive tool to monitor neuroplastic changes in the visual cortex of amblyopic children during the recovery of visual acuity in the amblyopic eye caused by the occlusion of the fellow eye.

In conclusion, taking advantage of the peculiar features of binocular rivalry detailed above, we have been able to reveal novel properties of early visual cortex such as residual plasticity and early cross-modal processing.

Taken together, our results have important implications for understanding the consequences of sensory loss on the adult visual system, suggesting that the recruitment of primary visual cortex for the processing of information from other sensory modalities observed in blind patients occurs by unmasking pre-existing connections from those modalities to the primary visual cortex, rather than in creating them ex-novo.

Finally, our deprivation studies also show that the adult visual cortex retains a higher degree of residual experience-dependent plasticity than previously thoutght. These results strongly suggest that the first response of the adult visual system to deprivation is a compensatory homeostatic boost of neural activity, probably occurring through up-regulation of contrast gain control mechanisms, as a first attempt to compensate for the impoverished incoming information provoked by visual deprivation.

References

Adams, R. J., Maurer, D., & Davis, M. (1986). Newborns' discrimination of chromatic from achromatic stimuli. *J Exp Child Psychol, 41*(2), 267-281.

Afra, J., Mascia, A., Gerard, P., Maertens de Noordhout, A., & Schoenen, J. (1998). Interictal cortical excitability in migraine: a study using transcranial magnetic stimulation of motor and visual cortices. *Ann Neurol, 44*(2), 209-215.

Alais, D. (2012). Binocular Rivalry: competition and inhibition in visual perception. *WIREs Cogn Sci . , 3*, 87-103.

Alais, D., & Blake, R. (2005). *Binocular Rivalry*. Cambridge, Massachusetts; London, England: MIT Press.

Alais, D., & Burr, D. (2003). The "Flash-Lag" effect occurs in audition and cross-modally. *Curr Biol, 13*(1), 59-63.

Alais, D., & Burr, D. (2004). The ventriloquist effect results from near-optimal bimodal integration. *Curr Biol, 14*(3), 257-262.

Alais, D., Cass, J., O'Shea, R. P., & Blake, R. (2010). Visual sensitivity underlying changes in visual consciousness. *Curr Biol, 20*(15), 1362-1367.

Alais, D., Lorenceau, J., Arrighi, R., & Cass, J. (2006). Contour interactions between pairs of Gabors engaged in binocular rivalry reveal a map of the association field. *Vision Res, 46*(8-9), 1473-1487.

Alais, D., & Melcher, D. (2007). Strength and coherence of binocular rivalry depends on shared stimulus complexity. *Vision Res, 47*(2), 269-279.

Alais, D., Newell, F. N., & Mamassian, P. (2010). Multisensory processing in review: from physiology to behaviour. *Seeing Perceiving, 23*(1), 3-38.

Alais, D., & Parker, A. (2006). Independent binocular rivalry processes for motion and form. *Neuron, 52*(5), 911-920.

Alais, D., van Boxtel, J. J., Parker, A., & van Ee, R. (2010). Attending to auditory signals slows visual alternations in binocular rivalry. *Vision Res, 50*(10), 929-935.

Almeida, J., Mahon, B. Z., Nakayama, K., & Caramazza, A. (2008). Unconscious processing dissociates along categorical lines. *Proc Natl Acad Sci U S A, 105*(39), 15214-15218.

Amedi, A., Floel, A., Knecht, S., Zohary, E., & Cohen, L. G. (2004). Transcranial magnetic stimulation of the occipital pole interferes with verbal processing in blind subjects. *Nat Neurosci, 7*(11), 1266-1270.

Amedi, A., Jacobson, G., Hendler, T., Malach, R., & Zohary, E. (2002). Convergence of visual and tactile shape processing in the human lateral occipital complex. *Cereb Cortex, 12*(11), 1202-1212.

Amedi, A., Malach, R., Hendler, T., Peled, S., & Zohary, E. (2001). Visuo-haptic object-related activation in the ventral visual pathway. *Nat Neurosci, 4*(3), 324-330.

Claudia Lunghi, *Early cross-modal interactions and adult human visual cortical plasticity revealed by binocular rivalry*
ISBN 978-88-6655-686-2 (print) ISBN 978-88-6655-687-9 (online),

Amedi, A., Raz, N., Pianka, P., Malach, R., & Zohary, E. (2003). Early 'visual' cortex activation correlates with superior verbal memory performance in the blind. *Nat Neurosci, 6*(7), 758-766.

Andersen, R. A., Essick, G. K., & Siegel, R. M. (1985). Encoding of spatial location by posterior parietal neurons. *Science, 230*(4724), 456-458.

Andrews, T. J., & Blakemore, C. (1999). Form and motion have independent access to consciousness. *Nat Neurosci, 2*(5), 405-406.

Andrews, T. J., & Purves, D. (1997). Similarities in normal and binocularly rivalrous viewing. *Proc Natl Acad Sci U S A, 94*(18), 9905-9908.

Anstis, S., & Ramachandran, V. S. (1987). Visual inertia in apparent motion. *Vision Res, 27*(5), 755-764.

Arabzadeh, E., Clifford, C. W., & Harris, J. A. (2008). Vision merges with touch in a purely tactile discrimination. *Psychol Sci, 19*(7), 635-641.

Arnold, D. H., James, B., & Roseboom, W. (2009). Binocular rivalry: spreading dominance through complex images. *J Vis, 9*(13), 4 1-9.

Atkinson, J., Hood, B., Wattam-Bell, J., Anker, S., & Tricklebank, J. (1988). Development of orientation discrimination in infancy. *Perception, 17*(5), 587-595.

Aurora, S. K., Ahmad, B. K., Welch, K. M., Bhardhwaj, P., & Ramadan, N. M. (1998). Transcranial magnetic stimulation confirms hyperexcitability of occipital cortex in migraine. *Neurology, 50*(4), 1111-1114.

Avillac, M., Ben Hamed, S., & Duhamel, J. R. (2007). Multisensory integration in the ventral intraparietal area of the macaque monkey. *J Neurosci, 27*(8), 1922-1932.

Avillac, M., Deneve, S., Olivier, E., Pouget, A., & Duhamel, J. R. (2005). Reference frames for representing visual and tactile locations in parietal cortex. *Nat Neurosci, 8*(7), 941-949.

Baccus, S. A., & Meister, M. (2002). Fast and slow contrast adaptation in retinal circuitry. *Neuron, 36*(5), 909-919.

Baker, C. I., Peli, E., Knouf, N., & Kanwisher, N. G. (2005). Reorganization of visual processing in macular degeneration. *J Neurosci, 25*(3), 614-618.

Baker, D. H. (2010). Visual consciousness: the binocular rivalry explosion. *Curr Biol, 20*(15), R644-646.

Baker, D. H., Meese, T. S., & Hess, R. F. (2008). Contrast masking in strabismic amblyopia: attenuation, noise, interocular suppression and binocular summation. *Vision Res, 48*(15), 1625-1640.

Banks, M. S., Aslin, R. N., & Letson, R. D. (1975). Sensitive period for the development of human binocular vision. *Science, 190*(4215), 675-677.

Banks, M. S., & Bennett, P. J. (1988). Optical and photoreceptor immaturities limit the spatial and chromatic vision of human neonates. *J Opt Soc Am A, 5*(12), 2059-2079.

Banton, T., & Bertenthal, B. I. (1996). Infants' sensitivity to uniform motion. *Vision Res, 36*(11), 1633-1640.

Bao, M., & Engel, S. A. (2012). Distinct mechanism for long-term contrast adaptation. *Proc Natl Acad Sci U S A, 109*(15), 5898-5903.

Bartels, A., & Logothetis, N. K. (2010). Binocular rivalry: a time dependence of eye and stimulus contributions. *J Vis, 10*(12), 3.

Beauchamp, M. S., Lee, K. E., Argall, B. D., & Martin, A. (2004). Integration of auditory and visual information about objects in superior temporal sulcus. *Neuron, 41*(5), 809-823.

Beauchamp, M. S., Yasar, N. E., Frye, R. E., & Ro, T. (2008). Touch, sound and vision in human superior temporal sulcus. *Neuroimage, 41*(3), 1011-1020.

Benevento, L. A., Fallon, J., Davis, B. J., & Rezak, M. (1977). Auditory--visual interaction in single cells in the cortex of the superior temporal sulcus and the orbital frontal cortex of the macaque monkey. *Exp Neurol, 57*(3), 849-872.

Berardi, N., Pizzorusso, T., & Maffei, L. (2000). Critical periods during sensory development. *Curr Opin Neurobiol, 10*(1), 138-145.

Bertelson, P., & Aschersleben, G. (1998). Automatic visual bias of perceived auditory location. *Psych. Bull. Rev., 5*, 482-489.

Birch, E. E., Stager, D., Leffler, J., & Weakley, D. (1998). Early treatment of congenital unilateral cataract minimizes unequal competition. *Invest Ophthalmol Vis Sci, 39*(9), 1560-1566.

Birch, E. E., & Stager, D. R. (1996). The critical period for surgical treatment of dense congenital unilateral cataract. *Invest Ophthalmol Vis Sci, 37*(8), 1532-1538.

Birch, E. E., Swanson, W. H., Stager, D. R., Woody, M., & Everett, M. (1993). Outcome after very early treatment of dense congenital unilateral cataract. *Invest Ophthalmol Vis Sci, 34*(13), 3687-3699.

Blake, R. (1977). Threshold conditions for binocular rivalry. *J Exp Psychol Hum Percept Perform, 3*(2), 251-257.

Blake, R. (1988). Dichoptic reading: the role of meaning in binocular rivalry. *Percept Psychophys, 44*(2), 133-141.

Blake, R. (1989). A neural theory of binocular rivalry. *Psychol Rev, 96*(1), 145-167.

Blake, R. (1997). What can be "perceived" in the absence of visual awareness? *Current Directions in Psychological Science, 6*(6), 157-162.

Blake, R. (2001). A primer on binocular rivalry, including current controversies. *Brain and Mind, 2*, 5-38.

Blake, R., Ahlstrom, U., & Alais, D. (1999). Perceptual priming by invisible motion. *Psychol Sci, 10*, 145-150.

Blake, R., & Fox, R. (1974a). Adaptation to invisible gratings and the site of binocular rivalry suppression. *Nature, 249*(456), 488-490.

Blake, R., & Fox, R. (1974b). Binocular rivalry suppression: insensitive to spatial frequency and orientation change. *Vision Res, 14*, 687-698.

Blake, R., & Fox, R. (1974c). Binocular rivalry suppression: insensitive to spatial frequency and orientation change. *Vision Res, 14*(8), 687-692.

Blake, R., & Logothetis, N. K. (2002). Visual competition. *Nat Rev Neurosci, 3*(1), 13-21.

Blake, R., O'Shea, R. P., & Mueller, T. J. (1992). Spatial zones of binocular rivalry in central and peripheral vision. *Vis Neurosci, 8*(5), 469-478.

Blake, R., Sobel, K. V., & James, T. W. (2004). Neural synergy between kinetic vision and touch. *Psychol Sci, 15*(6), 397-402.

Blake, R., Tadin, D., Sobel, K. V., Raissian, T. A., & Chong, S. C. (2006). Strength of early visual adaptation depends on visual awareness. *Proc Natl Acad Sci U S A, 103*(12), 4783-4788.

Blake, R., Westendorf, D., & Fox, R. (1990). Temporal perturbations of binocular rivalry. *Percept Psychophys, 48*(6), 593-602.

Blake, R., Yu, K., Lokey, M., & Norman, H. (1998). Binocular rivalry and motion perception. *J Cogn Neurosci, 10*(1), 46-60.

Blakemore, C. (1988). The sensitive periods of the monkey visual cortex. In G. Lennenstrand, G. K. Von Noorden & C. C. Campos (Eds.), *Strabismus and amblyopia: Experimental basis for advances in clinical management*. New York, NY: Plenum Press.

Blakemore, C., & Campbell, F. W. (1969). Adaptation to spatial stimuli. *J Physiol, 200*(1), 11P-13P.

Blakemore, C., Carpenter, R. H., & Georgeson, M. A. (1970). Lateral inhibition between orientation detectors in the human visual system. *Nature, 228*(5266), 37-39.

Blakemore, C., & Cooper, G. F. (1970). Development of the brain depends on the visual environment. *Nature, 228*(5270), 477-478.

Blakemore, C., Garey, L. J., & Vital-Durand, F. (1978). The physiological effects of monocular deprivation and their reversal in the monkey's visual cortex. *J Physiol, 283*, 223-262.

Blakemore, C., & Sutton, P. (1969). Size adaptation: a new aftereffect. *Science, 166*(3902), 245-247.

Blakemore, C., & Van Sluyters, R. C. (1974). Reversal of the physiological effects of monocular deprivation in kittens: further evidence for a sensitive period. *J Physiol, 237*(1), 195-216.

Blakemore, C., & Vital-Durand, F. (1983). Visual deprivation prevents the post-natal maturation of spatial contrast sensitivity neurons of the monkey's striate cortex. *J Physiol (London)*, 345-340.

Bonneh, Y., Sagi, D., & Karni, A. (2001). A transition between eye and object rivalry determined by stimulus coherence. *Vision Res, 41*(8), 981-989.

Boring, E. G. (1930). A new ambiguous figure. *The American Journal of Psychology, 42*(3), 444-445.

Born, R. T., & Bradley, D. C. (2005). Structure and function of visual area MT. *Annu Rev Neurosci, 28*, 157-189.

Boroojerdi, B., Battaglia, F., Muellbacher, W., & Cohen, L. G. (2001). Mechanisms underlying rapid experience-dependent plasticity in the human visual cortex. *Proc Natl Acad Sci U S A, 98*(25), 14698-14701.

Boroojerdi, B., Bushara, K. O., Corwell, B., Immisch, I., Battaglia, F., Muellbacher, W., et al. (2000). Enhanced excitability of the human visual cortex induced by short-term light deprivation. *Cereb Cortex, 10*(5), 529-534.

Bossink, C. J., Stalmeier, P. F., & De Weert, C. M. (1993). A test of Levelt's second proposition for binocular rivalry. *Vision Res, 33*(10), 1413-1419.

Boynton, G. M., Demb, J. B., Glover, G. H., & Heeger, D. J. (1999). Neuronal basis of contrast discrimination. *Vision Res, 39*(2), 257-269.

Bradley, A., Skottun, B. C., Ohzawa, I., Sclar, G., & Freeman, R. D. (1987). Visual orientation and spatial frequency discrimination: a comparison of single neurons and behavior. *J Neurophysiol, 57*(3), 755-772.

Brainard, D. H. (1997). The Psychophysics Toolbox. *Spat Vis, 10*(4), 433-436.

Brascamp, J. W., & Blake, R. (2012). Inattention abolishes binocular rivalry: perceptual evidence. *Psychol Sci, 23*(10), 1159-1167.

Brascamp, J. W., van Ee, R., Noest, A. J., Jacobs, R. H., & van den Berg, A. V. (2006). The time course of binocular rivalry reveals a fundamental role of noise. *J Vis, 6*(11), 1244-1256.

Bresciani, J. P., Dammeier, F., & Ernst, M. O. (2006). Vision and touch are automatically integrated for the perception of sequences of events. *J Vis, 6*(5), 554-564.

Bresciani, J. P., Ernst, M. O., Drewing, K., Bouyer, G., Maury, V., & Kheddar, A. (2005). Feeling what you hear: auditory signals can modulate tactile tap perception. *Exp Brain Res, 162*(2), 172-180.

Brown, R. J., & Norcia, A. M. (1997). A method for investigating binocular rivalry in real-time with the steady-state VEP. *Vision Res, 37*(17), 2401-2408.

Bruno, N., Jacomuzzi, A., Bertamini, M., & Meyer, G. (2007). A visual-haptic Necker cube reveals temporal constraints on intersensory merging during perceptual exploration. *Neuropsychologia, 45*(3), 469-475.

Bundesen, C., & Habekost, T. (2008). *Principles of Visual Attention: Linkng Mind and Brain.* Oxford: Oxford University Press.

Burton, H., Snyder, A. Z., Diamond, J. B., & Raichle, M. E. (2002). Adaptive changes in early and late blind: a FMRI study of verb generation to heard nouns. *J Neurophysiol, 88*(6), 3359-3371.

Calvert, G. A., Bullmore, E. T., Brammer, M. J., Campbell, R., Williams, S. C., McGuire, P. K., et al. (1997). Activation of auditory cortex during silent lipreading. *Science, 276*(5312), 593-596.

Calvert, G. A., Campbell, R., & Brammer, M. J. (2000). Evidence from functional magnetic resonance imaging of crossmodal binding in the human heteromodal cortex. *Curr Biol, 10*(11), 649-657.

Campanella, S., & Belin, P. (2007). Integrating face and voice in person perception. *Trends Cogn Sci, 11*(12), 535-543.

Candy, T. R., & Banks, M. S. (1999). Use of an early nonlinearity to measure optical and receptor resolution in the human infant. *Vision Res, 39*(20), 3386-3398.

Carpenter, R. H., & Blakemore, C. (1973). Interactions between orientations in human vision. *Exp Brain Res, 18*(3), 287-303.

Carrasco, M., Ling, S., & Read, S. (2004). Attention alters appearance. *Nat Neurosci, 7*(3), 308-313.

Carro, E., Nunez, A., Busiguina, S., & Torres-Aleman, I. (2000). Circulating insulin-like growth factor I mediates effects of exercise on the brain. *J Neurosci, 20*(8), 2926-2933.

Carter, O., & Cavanagh, P. (2007). Onset rivalry: brief presentation isolates an early independent phase of perceptual competition. *PLoS One, 2*(4), e343.

Carter, O., Konkle, T., Wang, Q., Hayward, V., & Moore, C. (2008). Tactile rivalry demonstrated with an ambiguous apparent-motion quartet. *Curr Biol, 18*(14), 1050-1054.

Carter, O., & Pettigrew, J. D. (2003). A common oscillator for perceptual rivalries? *Perception, 32*(3), 295-305.

Carulli, D., Pizzorusso, T., Kwok, J. C., Putignano, E., Poli, A., Forostyak, S., et al. (2010). Animals lacking link protein have attenuated perineuronal nets and persistent plasticity. *Brain, 133*(Pt 8), 2331-2347.

Cave, C., Blake, R., & McNamara, T. (1998). Binocular Rivalry distrupts visual priming. *Psychol Sci, 9*, 299-302.

Chen, Y. C., Yeh, S. L., & Spence, C. (2012). Crossmodal constraints on human perceptual awareness: auditory semantic modulation of binocular rivalry. *Front Psychol, 2*, 212.

Chong, S. C., & Blake, R. (2006). Exogenous attention and endogenous attention influence initial dominance in binocular rivalry. *Vision Res, 46*(11), 1794-1803.

Chong, S. C., Tadin, D., & Blake, R. (2005). Endogenous attention prolongs dominance durations in binocular rivalry. *J Vis, 5*(11), 1004-1012.

Chopin, A., & Mamassian, P. (2010). Usefulness influences visual appearance in motion transparency depth rivalry. *J Vis, 11*(7), 18.

Ciucci, F., Putignano, E., Baroncelli, L., Landi, S., Berardi, N., & Maffei, L. (2007). Insulin-like growth factor 1 (IGF-1) mediates the effects of enriched environment (EE) on visual cortical development. *PLoS One, 2*(5), e475.

Ciuffreda, K. J., Levi, D. M., & Selenow, A. (1991). *Amblyopia: basic and clinical aspects.* Stoneham, MA: Butterworth-Heinemann.

Clavagnier, S., Falchier, A., & Kennedy, H. (2004). Long-distance feedback projections to area V1: implications for multisensory integration, spatial awareness, and visual consciousness. *Cogn Affect Behav Neurosci, 4*(2), 117-126.

Clifford, C. W., Webster, M. A., Stanley, G. B., Stocker, A. A., Kohn, A., Sharpee, T. O., et al. (2007). Visual adaptation: neural, psychological and computational aspects. *Vision Res, 47*(25), 3125-3131.

Cohen, L. G., Celnik, P., Pascual-Leone, A., Corwell, B., Falz, L., Dambrosia, J., et al. (1997). Functional relevance of cross-modal plasticity in blind humans. *Nature, 389*(6647), 180-183.

Cohen, Y. E., Batista, A. P., & Andersen, R. A. (2002). Comparison of neural activity preceding reaches to auditory and visual stimuli in the parietal reach region. *Neuroreport, 13*(6), 891-894.

Conrad, V., Bartels, A., Kleiner, M., & Noppeney, U. (2010). Audiovisual interactions in binocular rivalry. *J Vis, 10*(10), 27.

Conrad, V., Vitello, M. P., & Noppeney, U. (2012). Interactions between apparent motion rivalry in vision and touch. *Psychol Sci, 23*(8), 940-948.

Corbetta, M., Kincade, J. M., & Shulman, G. L. (2002). Neural systems for visual orienting and their relationships to spatial working memory. *J Cogn Neurosci, 14*(3), 508-523.

Corbetta, M., & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci, 3*(3), 201-215.

Cosmelli, D., David, O., Lachaux, J. P., Martinerie, J., Garnero, L., Renault, B., et al. (2004). Waves of consciousness: ongoing cortical patterns during binocular rivalry. *Neuroimage, 23*(1), 128-140.

Craik, F. (1940). Origin of visual after-image. *Nature, 145*, 512.

Crawford, M. L., Blake, R., Cool, S. J., & von Noorden, G. K. (1975). Physiological consequences of unilateral and bilateral eye closure in macaque monkeys: some further observations. *Brain Res, 84*(1), 150-154.

Crawford, M. L., Pesch, T. W., von Noorden, G. K., Harwerth, R. S., & Smith, E. L. (1991). Bilateral form deprivation in monkeys. Electrophysiologic and anatomic consequences. *Invest Ophthalmol Vis Sci, 32*(8), 2328-2336.

Crick, F., & Koch, C. (1995). Are we aware of neural activity in primary visual cortex? *Nature, 375*(6527), 121-123.

Crick, F., & Koch, C. (1998). Consciousness and neuroscience. *Cereb Cortex, 8*(2), 97-107.

Crognale, M. A. (2002). Development, maturation, and aging of chromatic visual pathways: VEP results. *J Vis, 2*(6), 438-450.

Dakin, S., Carlin, P., & Hemsley, D. (2005). Weak suppression of visual context in chronic schizophrenia. *Curr Biol, 15*(20), R822-824.

de Jong, M. C., Knapen, T., & van Ee, R. (2012). Opposite influence of perceptual memory on initial and prolonged perception of sensory ambiguity. *PLoS One, 7*(1), e30595.

de Labra, C., & Valle-Inclan, F. (2001). Electrical activity in primary visual area due to interocular suppression. *Neuroreport, 12*(18), 4099-4102.

De Marco, A., Penengo, P., & Trabucco, A. (1977). Stochastic models and fluctuations in reversal time of ambiguous figures. *Perception, 6*(6), 645-656.

Denison, R. N., Piazza, E. A., & Silver, M. A. (2011). Predictive Context Influences Perceptual Selection during Binocular Rivalry. *Front Hum Neurosci, 5*, 166.

Denison, R. N., & Silver, M. A. (2012). Distinct contributions of the magnocellular and parvocellular visual streams to perceptual selection. *J Cogn Neurosci, 24*(1), 246-259.

Desimone, R., & Duncan, J. (1995). Neural mechanisms of selective visual attention. *Annu Rev Neurosci, 18*, 193-222.

Desmurget, M., Vindras, P., Grea, H., Viviani, P., & Grafton, S. T. (2000). Proprioception does not quickly drift during visual occlusion. *Exp Brain Res, 134*(3), 363-377.

Dilks, D. D., Serences, J. T., Rosenau, B. J., Yantis, S., & McCloskey, M. (2007). Human adult cortical reorganization and consequent visual distortion. *J Neurosci, 27*(36), 9585-9594.

Dobbins, A. C., & Grossmann, J. K. (2010). Asymmetries in perception of 3D orientation. *PLoS One, 5*(3), e9553.

Driver, J., & Noesselt, T. (2008). Multisensory interplay reveals crossmodal influences on 'sensory-specific' brain regions, neural responses, and judgments. *Neuron, 57*(1), 11-23.

Duensing, S., & Miller, B. (1979). The Cheshire Cat effect. *Perception, 8*(3), 269-273.

El Mallah, M. K., Chakravarthy, U., & Hart, P. M. (2000). Amblyopia: is visual loss permanent? *Br J Ophthalmol, 84*(9), 952-956.

Ellemberg, D., Lewis, T. L., Dirks, M., Maurer, D., Ledgeway, T., Guillemot, J. P., et al. (2004). Putting order into the development of sensitivity to global motion. *Vision Res, 44*(20), 2403-2411.

Ellemberg, D., Lewis, T. L., Liu, C. H., & Maurer, D. (1999). Development of spatial and temporal vision during childhood. *Vision Res, 39*(14), 2325-2333.

Ellemberg, D., Lewis, T. L., Maurer, D., Brar, S., & Brent, H. P. (2002). Better perception of global motion after monocular than after binocular deprivation. *Vision Res, 42*(2), 169-179.

Ellemberg, D., Lewis, T. L., Maurer, D., & Brent, H. P. (2000). Influence of monocular deprivation during infancy on the later development of spatial and temporal vision. *Vision Res, 40*(23), 3283-3295.

Ellemberg, D., Lewis, T. L., Maurer, D., Lui, C. H., & Brent, H. P. (1999). Spatial and temporal vision in patients treated for bilateral congenital cataracts. *Vision Res, 39*(20), 3480-3489.

Elman, J. L., Bates, E. A., Johnson, M. H., Kalmiloff-Smith, A., Parisi, D., & Plunket, K. (1996). *Rethinkinh innateness. A connectionist perspective on development*. Cambridge, MA: MIT Press.

Epstein, R., & Kanwisher, N. (1998). A cortical representation of the local visual environment. *Nature, 392*(6676), 598-601.

Ernst, M. O., & Banks, M. S. (2002). Humans integrate visual and haptic information in a statistically optimal fashion. *Nature, 415*(6870), 429-433.

Ernst, M. O., Banks, M. S., & Bulthoff, H. H. (2000). Touch can change visual slant perception. *Nat Neurosci, 3*(1), 69-73.

Ernst, M. O., & Bulthoff, H. H. (2004). Merging the senses into a robust percept. *Trends Cogn Sci, 8*(4), 162-169.

Fagiolini, M., Fritschy, J. M., Low, K., Mohler, H., Rudolph, U., & Hensch, T. K. (2004). Specific GABAA circuits for visual cortical plasticity. *Science, 303*(5664), 1681-1683.

Fagiolini, M., & Hensch, T. K. (2000). Inhibitory threshold for critical-period activation in primary visual cortex. *Nature, 404*(6774), 183-186.

Fagiolini, M., Pizzorusso, T., Berardi, N., Domenici, L., & Maffei, L. (1994). Functional postnatal development of the rat primary visual cortex and the role of visual experience: dark rearing and monocular deprivation. *Vision Res, 34*(6), 709-720.

Fahle, M. (1982). Binocular rivalry: suppression depends on orientation and spatial frequency. *Vision Res, 22*(7), 787-800.

Falchier, A., Clavagnier, S., Barone, P., & Kennedy, H. (2002). Anatomical evidence of multimodal integration in primate striate cortex. *J Neurosci, 22*(13), 5749-5759.

Fang, F., & He, S. (2005). Cortical responses to invisible objects in the human dorsal and ventral pathways. *Nat Neurosci, 8*(10), 1380-1385.

Fantz, R. L. (1963). Pattern Vision in Newborn Infants. *Science, 140*(3564), 296-297.

Fantz, R. L., Ordy, J. M., & Udelf, M. S. (1962). Maturation of pattern vision in infants during the first six months. *J Comp Physiol Psychol, 55*, 907-917.

Felleman, D. J., & Van Essen, D. C. (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cereb Cortex, 1*(1), 1-47.

Fendrich, R., & Corballis, P. M. (2001). The temporal cross-capture of audition and vision. *Percept Psychophys, 63*(4), 719-725.

Fine, I., Smallman, H. S., Doyle, P., & MacLeod, D. I. (2002). Visual function before and after the removal of bilateral congenital cataracts in adulthood. *Vision Res, 42*(2), 191-210.

Fine, I., Wade, A. R., Brewer, A. A., May, M. G., Goodman, D. F., Boynton, G. M., et al. (2003). Long-term deprivation affects visual perception and cortex. *Nat Neurosci, 6*(9), 915-916.

Finney, E. M., Fine, I., & Dobkins, K. R. (2001). Visual stimuli activate auditory cortex in the deaf. *Nat Neurosci, 4*(12), 1171-1173.

Fitzgerald, P. J., Lane, J. W., Thakur, P. H., & Hsiao, S. S. (2006). Receptive field properties of the macaque second somatosensory cortex: representation of orientation on different finger pads. *J Neurosci, 26*(24), 6473-6484.

Fox, R., & Check, R. (1968). Detection of motion during binocular rivalry suppression. *J Exp Psychol, 78*, 388-395.

Fox, R., & J., H. (1967). Stochastic properties of binocular rivalry alternations. *Percept Psychophys, 2*, 432-436.

Fox, R., & Rasche, F. (1969). Binocualr rivalry and reciprocal inhibition. *Percept Psychophys, 5*, 215-217.

Foxe, J. J., Wylie, G. R., Martinez, A., Schroeder, C. E., Javitt, D. C., Guilfoyle, D., et al. (2002). Auditory-somatosensory multisensory processing in auditory association cortex: an fMRI study. *J Neurophysiol, 88*(1), 540-543.

Franklin, A., & Davies, I. R. (2004). New evidence for infant colour categories. *Br J Dev Psychol, 22*, 344-377.

Freeman, A. W., Nguyen, V. A., & Alais, D. (2005). The Nature and Depth of Binocular Rivalry Suppression. In D. Alais & R. Blake (Eds.), *Binocular Rivalry* (pp. 47-62). Cambridge, Massachusetts: The MIT Press.

Frenkel, M. Y., & Bear, M. F. (2004). How monocular deprivation shifts ocular dominance in visual cortex of young mice. *Neuron, 44*(6), 917-923.

Frisby, J. P. (1979). *Seeing: Illusion, Brain and Mind*. Oxford: Oxford University Press.

Fu, K. M., Johnston, T. A., Shah, A. S., Arnold, L., Smiley, J., Hackett, T. A., et al. (2003). Auditory cortical neurons respond to somatosensory stimulation. *J Neurosci, 23*(20), 7510-7515.

Gegenfurtner, K. R., & Kiper, D. C. (2003). Color vision. *Annu Rev Neurosci, 26*, 181-206.

Genc, E., Bergmann, J., Singer, W., & Kohler, A. (2011). Interhemispheric connections shape subjective experience of bistable motion. *Curr Biol, 21*(17), 1494-1499.

Genc, E., Bergmann, J., Tong, F., Blake, R., Singer, W., & Kohler, A. (2011). Callosal connections of primary visual cortex predict the spatial spreading of binocular rivalry across the visual hemifields. *Front Hum Neurosci, 5*, 161.

Gepshtein, S., & Banks, M. S. (2003). Viewing geometry determines how vision and haptics combine in size perception. *Curr Biol, 13*(6), 483-488.

Gepshtein, S., Burge, J., Ernst, M. O., & Banks, M. S. (2005). The combination of vision and touch depends on spatial proximity. *J Vis, 5*(11), 1013-1023.

Ghazanfar, A. A., Maier, J. X., Hoffman, K. L., & Logothetis, N. K. (2005). Multisensory integration of dynamic faces and voices in rhesus monkey auditory cortex. *J Neurosci, 25*(20), 5004-5012.

Ghazanfar, A. A., & Schroeder, C. E. (2006). Is neocortex essentially multisensory? *Trends Cogn Sci, 10*(6), 278-285.

Gianfranceschi, L., Siciliano, R., Walls, J., Morales, B., Kirkwood, A., Huang, Z. J., et al. (2003). Visual cortex is rescued from the effects of dark rearing by overexpression of BDNF. *Proc Natl Acad Sci U S A, 100*(21), 12486-12491.

Gibson, J. J., & Radner, M. (1937). Adaptation, aftereffect and contrast in the perception of tilted lines. *J Exp Psychol, 20*(453-467).

Gilbert, C. D., Hirsch, J. A., & Wiesel, T. N. (1990). Lateral interactions in visual cortex. *Cold Spring Harb Symp Quant Biol, 55*, 663-677.

Gilbert, C. D., & Li, W. (2012). Adult visual cortical plasticity. *Neuron, 75*(2), 250-264.

Gilroy, L. A., & Blake, R. (2005). The interaction between binocular rivalry and negative afterimages. *Curr Biol, 15*(19), 1740-1744.

Goodale, M. A., & Milner, A. D. (1992). Separate visual pathways for perception and action. *Trends Neurosci, 15*(1), 20-25.

Gordon, J. A., & Stryker, M. P. (1996). Experience-dependent plasticity of binocular responses in the primary visual cortex of the mouse. *J Neurosci, 16*(10), 3274-3286.

Gori, M., Del Viva, M., Sandini, G., & Burr, D. C. (2008). Young children do not integrate visual and haptic form information. *Curr Biol, 18*(9), 694-698.

Gori, M., Mazzilli, G., Sandini, G., & Burr, D. (2011). Cross-Sensory Facilitation Reveals Neural Interactions between Visual and Tactile Motion in Humans. *Front Psychol, 2*, 55.

Goyal, M. S., Hansen, P. J., & Blakemore, C. B. (2006). Tactile perception recruits functionally related visual areas in the late-blind. *Neuroreport, 17*(13), 1381-1384.

Gray, K. L., Adams, W. J., & Garner, M. (2009). The influence of anxiety on the initial selection of emotional faces presented in binocular rivalry. *Cognition, 113*(1), 105-110.

Grill-Spector, K., Kushnir, T., Edelman, S., Itzchak, Y., & Malach, R. (1998). Cue-invariant activation in object-related areas of the human occipital lobe. *Neuron, 21*(1), 191-202.

Grill-Spector, K., Kushnir, T., Hendler, T., & Malach, R. (2000). The dynamics of object-selective activation correlate with recognition performance in humans. *Nat Neurosci, 3*(8), 837-843.

Gunn, A., Cory, E., Atkinson, J., Braddick, O., Wattam-Bell, J., Guzzetta, A., et al. (2002). Dorsal and ventral stream sensitivity in normal development and hemiplegia. *Neuroreport, 13*(6), 843-847.

Guzman-Martinez, E., Ortega, L., Grabowecky, M., Mossbridge, J., & Suzuki, S. (2012a). Interactive coding of visual spatial frequency and auditory amplitude-modulation rate. *Curr Biol, 22*(5), 383-388.

Guzman-Martinez, E., Ortega, L., Grabowecky, M., Mossbridge, J., & Suzuki, S. (2012b). Interactive Coding of Visual Spatial Frequency and Auditory Amplitude-Modulation Rate. *Curr Biol.*

Hamilton, R., Keenan, J. P., Catala, M., & Pascual-Leone, A. (2000). Alexia for Braille following bilateral occipital stroke in an early blind woman. *Neuroreport, 11*(2), 237-240.

Hancock, S., & Andrews, T. J. (2007). The role of voluntary and involuntary attention in selecting perceptual dominance during binocular rivalry. *Perception, 36*(2), 288-298.

Hanover, J. L., Huang, Z. J., Tonegawa, S., & Stryker, M. P. (1999). Brain-derived neurotrophic factor overexpression induces precocious critical period in mouse visual cortex. *J Neurosci, 19*(22), RC40.

Hansen, C. H., & Hansen, R. D. (1988). Finding the face in the crownd: An face-in-the-crowd effect. *Journal of Personality and Social Psychology, 54*, 917-924.

Harauzov, A., Spolidoro, M., DiCristo, G., De Pasquale, R., Cancedda, L., Pizzorusso, T., et al. (2010). Reducing intracortical inhibition in the adult visual cortex promotes ocular dominance plasticity. *J Neurosci, 30*(1), 361-371.

Harwerth, R. S., Smith, E. L., 3rd, Duncan, G. C., Crawford, M. L., & von Noorden, G. K. (1986). Multiple sensitive periods in the development of the primate visual system. *Science, 232*(4747), 235-238.

Harwerth, R. S., Smith, E. L., 3rd, Paul, A. D., Crawford, M. L., & von Noorden, G. K. (1991). Functional effects of bilateral form deprivation in monkeys. *Invest Ophthalmol Vis Sci, 32*(8), 2311-2327.

Haynes, J. D., Deichmann, R., & Rees, G. (2005). Eye-specific effects of binocular rivalry in the human lateral geniculate nucleus. *Nature, 438*(7067), 496-499.

Haynes, J. D., & Rees, G. (2005). Predicting the stream of consciousness from activity in human visual cortex. *Curr Biol, 15*(14), 1301-1307.

Heimel, J. A., van Versendaal, D., & Levelt, C. N. (2012). The role of GABAergic inhibition in ocular dominance plasticity. *Neural Plast, 2011*, 391763.

Hein, G., Doehrmann, O., Muller, N. G., Kaiser, J., Muckli, L., & Naumer, M. J. (2007). Object familiarity and semantic congruency modulate responses in cortical audiovisual integration areas. *J Neurosci, 27*(30), 7881-7887.

Helbig, H. B., & Ernst, M. O. (2007). Optimal integration of shape information from vision and touch. *Exp Brain Res, 179*(4), 595-606.

Helmoltz, H. (1925). *Treatise on physiological optics*. New York: Dover: J. PC. Southall

Hendry, S. H., & Jones, E. G. (1986). Reduction in number of immunostained GABAergic neurones in deprived-eye dominance columns of monkey area 17. *Nature, 320*(6064), 750-753.

Hensch, T. K. (2004). Critical period regulation. *Annu Rev Neurosci, 27*, 549-579.

Hensch, T. K., Fagiolini, M., Mataga, N., Stryker, M. P., Baekkeskov, S., & Kash, S. F. (1998). Local GABA circuit control of experience-dependent plasticity in developing visual cortex. *Science, 282*(5393), 1504-1508.

Hillis, J. M., Ernst, M. O., Banks, M. S., & Landy, M. S. (2002). Combining sensory information: mandatory fusion within, but not between, senses. *Science, 298*(5598), 1627-1630.

Hirsch, H. V., & Spinelli, D. N. (1970). Visual experience modifies distribution of horizontally and vertically oriented receptive fields in cats. *Science, 168*(3933), 869-871.

Hofer, S. B., Mrsic-Flogel, T. D., Bonhoeffer, T., & Hubener, M. (2006). Prior experience enhances plasticity in adult visual cortex. *Nat Neurosci, 9*(1), 127-132.

Hollins, M. (1980). The effect of contrast on the completeness of binocular rivalry suppression. *Percept Psychophys, 27*(6), 550-556.

Hong, S. W., & Shevell, S. K. (2009). Color-binding errors during rivalrous suppression of form. *Psychol Sci, 20*(9), 1084-1091.

Horton, J. C., & Hocking, D. R. (1997). Timing of the critical period for plasticity of ocular dominance columns in macaque striate cortex. *J Neurosci, 17*(10), 3684-3709.

Howard, I. P., & Templeton, W. B. (1966). *Human Spatial orientation*. New York, USA: Wiley.

Hsiao, S. S., Lane, J., & Fitzgerald, P. (2002). Representation of orientation in the somatosensory system. *Behav Brain Res, 135*(1-2), 93-103.

Hu, B., & Knill, D. C. (2010). Kinesthetic information disambiguates visual motion signals. *Curr Biol, 20*(10), R436-437.

Huang, Z. J., Kirkwood, A., Pizzorusso, T., Porciatti, V., Morales, B., Bear, M. F., et al. (1999). BDNF regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex. *Cell, 98*(6), 739-755.

Hubel, D. H., & Livingstone, M. S. (1990). Color and contrast sensitivity in the lateral geniculate body and primary visual cortex of the macaque monkey. *J Neurosci, 10*(7), 2223-2237.

Hubel, D. H., & Wiesel, T. N. (1962). Receptive fields, binocular interaction and functional architecture in the cat's visual cortex. *J Physiol, 160*, 106-154.

Hubel, D. H., & Wiesel, T. N. (1963). Receptive Fields of Cells in Striate Cortex of Very Young, Visually Inexperienced Kittens. *J Neurophysiol, 26*, 994-1002.

Hubel, D. H., & Wiesel, T. N. (1964). Effects of Monocular Deprivation in Kittens. *Naunyn Schmiedebergs Arch Exp Pathol Pharmakol, 248*, 492-497.

Hubel, D. H., & Wiesel, T. N. (1970). The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *J Physiol, 206*(2), 419-436.

Hubel, D. H., & Wiesel, T. N. (1977). Ferrier lecture. Functional architecture of macaque monkey visual cortex. *Proc R Soc Lond B Biol Sci, 198*(1130), 1-59.

Hubel, D. H., Wiesel, T. N., & LeVay, S. (1977). Plasticity of ocular dominance columns in monkey striate cortex. *Philos Trans R Soc Lond B Biol Sci, 278*(961), 377-409.

Hubel, D. H., Wiesel, T. N., & Stryker, M. P. (1977). Orientation columns in macaque monkey visual cortex demonstrated by the 2-deoxyglucose autoradiographic technique. *Nature, 269*(5626), 328-330.

Hudak, M., Gervan, P., Friedrich, B., Pastukhov, A., Braun, J., & Kovacs, I. (2011). Increased readiness for adaptation and faster alternation rates under binocular rivalry in children. *Front Hum Neurosci, 5*, 128.

Huk, A. C., Ress, D., & Heeger, D. J. (2001). Neuronal basis of the motion aftereffect reconsidered. *Neuron, 32*(1), 161-172.

Humphrey, G. K., & Goodale, M. A. (1998). Probing unconscious visual processing with the McCollough effect. *Conscious Cogn, 7*(3), 494-519.

Huttenlocher, P. R. (1984). Synapse elimination and plasticity in developing human cerebral cortex. *Am J Ment Defic, 88*(5), 488-496.

Huttenlocher, P. R., de Courten, C., Garey, L. J., & Van der Loos, H. (1982). Synaptogenesis in human visual cortex--evidence for synapse elimination during normal development. *Neurosci Lett, 33*(3), 247-252.

Iacobucci, I. L., Archer, S. M., Furr, B. A., Martonyi, E. J., & Del Monte, M. A. (2001). Bangerter foils in the treatment of moderate amblyopia. *Am Orthopt J, 51*, 84-91.

Issa, N. P., Trachtenberg, J. T., Chapman, B., Zahs, K. R., & Stryker, M. P. (1999). The critical period for ocular dominance plasticity in the Ferret's visual cortex. *J Neurosci, 19*(16), 6965-6978.

Jastrow, J. (1899). The Mind's Eye. *Popular Sci. Monthly, 54*, 299-312.

Jeffrey, B. G., Birch, E. E., Stager, D. R., Jr., Stager, D. R., Sr., & Weakley, D. R., Jr. (2001). Early binocular visual experience may improve binocular sensory outcomes in children after surgery for congenital unilateral cataract. *J Aapos, 5*(4), 209-216.

Jiang, Y., Costello, P., Fang, F., Huang, M., & He, S. (2006). A gender- and sexual orientation-dependent spatial attentional effect of invisible images. *Proc Natl Acad Sci U S A, 103*(45), 17048-17052.

Jiang, Y., & He, S. (2006). Cortical responses to invisible faces: dissociating subsystems for facial-information processing. *Curr Biol, 16*(20), 2023-2029.

Jones, E. G., & Powell, T. P. (1970). An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. *Brain, 93*(4), 793-820.

Kalisvaart, J. P., Rampersad, S. M., & Goossens, J. (2011). Binocular onset rivalry at the time of saccades and stimulus jumps. *PLoS One, 6*(6), e20017.

Kanai, R., Bahrami, B., & Rees, G. (2010). Human parietal cortex structure predicts individual differences in perceptual rivalry. *Curr Biol, 20*(18), 1626-1630.

Kang, M.-S., & Blake, R. (2005). Perceptual synergy between seeing and hearing revealed during binocular rivalry. *Psychologija, 32*.

Kang, M. S. (2009). Size matters: a study of binocular rivalry dynamics. *J Vis, 9*(1), 17 11-11.

Kang, M. S., & Blake, R. (2011). An integrated framework of spatiotemporal dynamics of binocular rivalry. *Front Hum Neurosci, 5*, 88.

Kang, M. S., Blake, R., & Woodman, G. F. (2011). Semantic analysis does not occur in the absence of awareness induced by interocular suppression. *J Neurosci, 31*(38), 13535-13545.

Kanwisher, N., McDermott, J., & Chun, M. M. (1997). The fusiform face area: a module in human extrastriate cortex specialized for face perception. *J Neurosci, 17*(11), 4302-4311.

Kapadia, M. K., Ito, M., Gilbert, C. D., & Westheimer, G. (1995). Improvement in visual sensitivity by changes in local context: parallel studies in human observers and in V1 of alert monkeys. *Neuron, 15*(4), 843-856.

Kaplan, E., Shapley, R. M., & Purpura, K. (1988). Color and luminance contrast as tools for probing the primate retina. *Neurosci Res Suppl, 8*, S151-165.

Kaplan, I. T., & Metlay, W. (1964). Light intensity and binocular rivalry. *J Exp Psychol, 67*, 22-26.

Karni, A., & Bertini, G. (1997). Learning perceptual skills: behavioral probes into adult cortical plasticity. *Curr Opin Neurobiol, 7*(4), 530-535.

Kastner, S., & Ungerleider, L. G. (2000). Mechanisms of visual attention in the human cortex. *Annu Rev Neurosci, 23*, 315-341.

Katz, L. C., & Shatz, C. J. (1996). Synaptic activity and the construction of cortical circuits. *Science, 274*(5290), 1133-1138.

Kauffman, T., Theoret, H., & Pascual-Leone, A. (2002). Braille character discrimination in blindfolded human subjects. *Neuroreport, 13*(5), 571-574.

Keck, T., Mrsic-Flogel, T. D., Vaz Afonso, M., Eysel, U. T., Bonhoeffer, T., & Hubener, M. (2008). Massive restructuring of neuronal circuits during functional reorganization of adult visual cortex. *Nat Neurosci, 11*(10), 1162-1167.

Keck, T., Scheuss, V., Jacobsen, R. I., Wierenga, C. J., Eysel, U. T., Bonhoeffer, T., et al. (2011). Loss of sensory input causes rapid structural changes of inhibitory neurons in adult mouse visual cortex. *Neuron, 71*(5), 869-882.

Kim, Y. J., Grabowecky, M., & Suzuki, S. (2006). Stochastic resonance in binocular rivalry. *Vision Res, 46*(3), 392-406.

Kiorpes, L., Kiper, D. C., O'Keefe, L. P., Cavanaugh, J. R., & Movshon, J. A. (1998). Neuronal correlates of amblyopia in the visual cortex of macaque monkeys with experimental strabismus and anisometropia. *J Neurosci, 18*(16), 6411-6424.

Kivlin, J. D., & Flynn, J. T. (1981). Therapy of anisometropic amblyopia. *J Pediatr Ophthalmol Strabismus, 18*(5), 47-56.

Kleinschmidt, A., Sterzer, P., & Rees, G. (2012). Variability of perceptual multistability: from brain state to individual trait. *Philos Trans R Soc Lond B Biol Sci, 367*(1591), 988-1000.

Klink, P. C., Brascamp, J. W., Blake, R., & van Wezel, R. J. (2010). Experience-driven plasticity in binocular vision. *Curr Biol, 20*(16), 1464-1469.

Klink, P. C., van Wezel, R. J., & van Ee, R. (2012). United we sense, divided we fail: context-driven perception of ambiguous visual stimuli. *Philos Trans R Soc Lond B Biol Sci, 367*(1591), 932-941.

Knapen, T., Brascamp, J., Pearson, J., van Ee, R., & Blake, R. (2011). The role of frontal and parietal brain areas in bistable perception. *J Neurosci, 31*(28), 10293-10301.

Knapen, T., Paffen, C., Kanai, R., & van Ee, R. (2007). Stimulus flicker alters interocular grouping during binocular rivalry. *Vision Res, 47*(1), 1-7.

Knill, D. C., & Pouget, A. (2004). The Bayesian brain: the role of uncertainty in neural coding and computation. *Trends Neurosci, 27*(12), 712-719.

Koch, C. (2007). *The quest for Consciousness: a neurobiological Approach*. Greenwood Village, CO: Roberts & Company.

Koffka, K. (1935). *Principles of Gestalt psychology*. London: Kegan, Paul, Trench & Trubner.

Kohn, A. (2007). Visual adaptation: physiology, mechanisms, and functional benefits. *J Neurophysiol, 97*(5), 3155-3164.

Kovacs, I., & Eisenberg, M. (2005). Human development of binocular rivalry. In D. Alais & R. Blake (Eds.), *Binocular Rivalry* (pp. 101-116). Cambridge: MIT Press.

Kovacs, I., Papathomas, T. V., Yang, M., & Feher, A. (1996). When the brain changes its mind: interocular grouping during binocular rivalry. *Proc Natl Acad Sci U S A, 93*(26), 15508-15511.

Kreiman, G., Fried, I., & Koch, C. (2002). Single-neuron correlates of subjective vision in the human medial temporal lobe. *Proc Natl Acad Sci U S A, 99*(12), 8378-8383.

Kugelberg, U. (1992). Visual acuity following treatment of bilateral congenital cataracts. *Doc Ophthalmol, 82*(3), 211-215.

Kujala, T., Alho, K., Kekoni, J., Hamalainen, H., Reinikainen, K., Salonen, O., et al. (1995). Auditory and somatosensory event-related brain potentials in early blind humans. *Exp Brain Res, 104*(3), 519-526.

Kupfer, C. (1957). Treatment of amblyopia exanopsia in adults; a preliminary report of seven cases. *Am J Ophthalmol, 43*(6), 918-922.

Kwon, M., Legge, G. E., Fang, F., Cheong, A. M., & He, S. (2009). Adaptive changes in visual cortex following prolonged contrast reduction. *J Vis, 9*(2), 20 21-16.

Lack, L. (1978). *Selective Attention and the Control of Binocular Rivalry*. Mouton: The Hague.

Lee, S. H., & Blake, R. (1999). Rival ideas about binocular rivalry. *Vision Res, 39*(8), 1447-1454.

Lee, S. H., Blake, R., & Heeger, D. J. (2005). Traveling waves of activity in primary visual cortex during binocular rivalry. *Nat Neurosci, 8*(1), 22-23.

Lee, S. H., Blake, R., & Heeger, D. J. (2007). Hierarchy of cortical responses underlying binocular rivalry. *Nat Neurosci, 10*(8), 1048-1054.

Lee, W. C., Huang, H., Feng, G., Sanes, J. R., Brown, E. N., So, P. T., et al. (2006). Dynamic remodeling of dendritic arbors in GABAergic interneurons of adult visual cortex. *PLoS Biol, 4*(2), e29.

Legge, G. E., & Foley, J. M. (1980). Contrast masking in human vision. *J Opt Soc Am, 70*(12), 1458-1471.

Lehky, S. R. (1988). An astable multivibrator model of binocular rivalry. *Perception, 17*(2), 215-228.

Lehky, S. R. (1995). Binocular rivalry is not chaotic. *Proc Biol Sci, 259*(1354), 71-76.

Leopold, D. A., & Logothetis, N. K. (1996). Activity changes in early visual cortex reflect monkeys' percepts during binocular rivalry. *Nature, 379*(6565), 549-553.

Leopold, D. A., & Logothetis, N. K. (1999). Multistable phenomena: changing views in perception. *Trends Cogn Sci, 3*(7), 254-264.

Leopold, D. A., O'Toole, A. J., Vetter, T., & Blanz, V. (2001). Prototype-referenced shape encoding revealed by high-level aftereffects. *Nat Neurosci, 4*(1), 89-94.

Leopold, D. A., Wilke, M., Maier, A., & Logothetis, N. K. (2002). Stable perception of visually ambiguous patterns. *Nat Neurosci, 5*(6), 605-609.

LeVay, S., Wiesel, T. N., & Hubel, D. H. (1980). The development of ocular dominance columns in normal and visually deprived monkeys. *J Comp Neurol, 191*(1), 1-51.

Levelt, W. J. (1965). *On Binocular Rivalry*. Soesterberg: Netherlands: Institution for Perception.

Levelt, W. J. (1966). The alternation process in binocular rivalry. *Br J Psychol, 57*(3 and 4), 225-238.

Levelt, W. J. (1967). Note on the distribution of dominance times in binocular rivalry. *Br J Psychol, 58*(1), 143-145.

Levi, D. M. (2005). Perceptual learning in adults with amblyopia: a reevaluation of critical periods in human vision. *Dev Psychobiol, 46*(3), 222-232.

Levi, D. M., & Carkeet, A. (1993). Amblyopia: a consequence of abnormal visual development. In K. Simons (Ed.), *Early Visual Development, Normal and Abnormal* (pp. 391-408). New York, NY: Oxford University Press.

Levi, D. M., & Li, R. W. (2009). Improving the performance of the amblyopic visual system. *Philos Trans R Soc Lond B Biol Sci, 364*(1515), 399-407.

Levi, D. M., McKee, S. P., & Movshon, J. A. (2011). Visual deficits in anisometropia. *Vision Res, 51*(1), 48-57.

Lewis, T. L., Ellemberg, D., Maurer, D., & Brent, H. P. (2000). Changes in spatial vision during middle childhood in patients treated for congenital cataracts. *Invest Ophthalmol Vis Sci, 41*, S726.

Lewis, T. L., Ellemberg, D., Maurer, D., Dirks, M., Wilkinson, F., & Wilson, H. R. (2004). A window on the normal development of sensitivity to global form in Glass patterns. *Perception, 33*(4), 409-418.

Lewis, T. L., Ellemberg, D., Maurer, D., Wilkinson, F., Wilson, H. R., Dirks, M., et al. (2002). Sensitivity to global form in glass patterns after early visual deprivation in humans. *Vision Res, 42*(8), 939-948.

Lewis, T. L., & Maurer, D. (2005). Multiple sensitive periods in human visual development: evidence from visually deprived children. *Dev Psychobiol, 46*(3), 163-183.

Lewis, T. L., Maurer, D., & Brent, H. P. (1995). Development of grating acuity in children treated for unilateral or bilateral congenital cataract. *Invest Ophthalmol Vis Sci, 36*(10), 2080-2095.

Lewis, T. L., Maurer, D., Tytla, M. E., Bowering, E. R., & Brent, H. P. (1992). Vision in the "good" eye of children treated for unilateral congenital cataract. *Ophthalmology, 99*(7), 1013-1017.

Lin, Z., & He, S. (2009). Seeing the invisible: the scope and limits of unconscious processing in binocular rivalry. *Prog Neurobiol, 87*(4), 195-211.

Ling, S., & Blake, R. (2009). Suppression during binocular rivalry broadens orientation tuning. *Psychol Sci, 20*(11), 1348-1355.

Logothetis, N. K. (1998). Single units and conscious vision. *Philos Trans R Soc Lond B Biol Sci, 353*(1377), 1801-1818.

Logothetis, N. K. (2003). The underpinnings of the BOLD functional magnetic resonance imaging signal. *J Neurosci, 23*(10), 3963-3971.

Logothetis, N. K., Leopold, D. A., & Sheinberg, D. L. (1996). What is rivalling during binocular rivalry? *Nature, 380*(6575), 621-624.

Logothetis, N. K., & Schall, J. D. (1989). Neuronal correlates of subjective visual perception. *Science, 245*(4919), 761-763.

Lumer, E. D., Friston, K. J., & Rees, G. (1998). Neural correlates of perceptual rivalry in the human brain. *Science, 280*(5371), 1930-1934.

Lundvall, A., & Kugelberg, U. (2002). Outcome after treatment of congenital unilateral cataract. *Acta Ophthalmol Scand, 80*(6), 588-592.

Lunghi, C., Binda, P., & Morrone, M. C. (2010). Touch disambiguates rivalrous perception at early stages of visual analysis. *Curr Biol, 20*(4), R143-144.

Lunghi, C., Burr, D. C., & Morrone, C. (2011). Brief periods of monocular deprivation disrupt ocular balance in human adult visual cortex. *Curr Biol, 21*(14), R538-539.

Luth, H. J., Fischer, J., & Celio, M. R. (1992). Soybean lectin binding neurons in the visual cortex of the rat contain parvalbumin and are covered by glial nets. *J Neurocytol, 21*(3), 211-221.

Macaluso, E., Frith, C. D., & Driver, J. (2000). Modulation of human visual cortex by crossmodal spatial attention. *Science, 289*(5482), 1206-1208.

MacLeod, D. I., & Boynton, R. M. (1979). Chromaticity diagram showing cone excitation by stimuli of equal luminance. *J Opt Soc Am, 69*(8), 1183-1186.

Maffei, L., & Fiorentini, A. (1973). The visual cortex as a spatial frequency analyser. *Vision Res, 13*(7), 1255-1267.

Magnusson, G., Abrahamsson, M., & Sjostrand, J. (2002). Changes in visual acuity from 4 to 12 years of age in children operated for bilateral congenital cataracts. *Br J Ophthalmol, 86*(12), 1385-1389.

Mamassian, P., & Goutcher, R. (2005). Temporal dynamics in bistable perception. *J Vis, 5*(4), 361-375.

Mandavilli, A. (2006). Visual neuroscience: look and learn. *Nature, 441*(7091), 271-272.

Marg, E., & Rudiak, D. (1994). Phosphenes induced by magnetic stimulation over the occipital brain: description and probable site of stimulation. *Optom Vis Sci, 71*(5), 301-311.

Maruya, K., Yang, E., & Blake, R. (2007). Voluntary action influences visual competition. *Psychol Sci, 18*(12), 1090-1098.

Mather, G., Verstraten, F. A., & Anstis, S. (1998). *The Motion Aftereffect: A Modern Perspective*. Cambridge, A: the MIT Press.

Maunsell, J. H., & Newsome, W. T. (1987). Visual processing in monkey extrastriate cortex. *Annu Rev Neurosci, 10*, 363-401.

Maunsell, J. H., & Van Essen, D. C. (1983). Functional properties of neurons in middle temporal visual area of the macaque monkey. II. Binocular interactions and sensitivity to binocular disparity. *J Neurophysiol, 49*(5), 1148-1167.

Maurer, D., Ellemberg, D., & Lewis, T. L. (2006). Repeated measurements of contrast sensitivity reveal limits to visual plasticity after early binocular deprivation in humans. *Neuropsychologia, 44*(11), 2104-2112.

Maurer, D., & Lewis, T. L. (2001a). VIsual acuity and spatial contrast sensitivity: normal development and underlying mechanisms. In C. A. Nelson & M. Luciana (Eds.), *The Handbook of Developmental COgnitive Neuroscience* (pp. 237-251). Cambridge, MA: MIT Press.

Maurer, D., & Lewis, T. L. (2001b). Visual acuity: the role of visual input in inducing postnatal changes. *Clin Neurosci Res, 1*, 239-247.

Maurer, D., Lewis, T. L., Brent, H. P., & Levin, A. V. (1999). Rapid improvement in the acuity of infants after visual input. *Science, 286*(5437), 108-110.

Maurer, D., Lewis, T. L., & Mondloch, C. J. (2005). Missing sights: consequences for visual cognitive development. *Trends Cogn Sci, 9*(3), 144-151.

Maurer, D., Mondloch, C. J., & Lewis, T. L. (2007). Sleeper effects. *Dev Sci, 10*(1), 40-47.

Maya Vetencourt, J. F., Sale, A., Viegi, A., Baroncelli, L., De Pasquale, R., O'Leary, O. F., et al. (2008). The antidepressant fluoxetine restores plasticity in the adult visual cortex. *Science, 320*(5874), 385-388.

Mayer, D. L., Beiser, A. S., Warner, A. F., Pratt, E. M., Raye, K. N., & Lang, J. M. (1995). Monocular acuity norms for the Teller Acuity Cards between ages one month and four years. *Invest Ophthalmol Vis Sci, 36*(3), 671-685.

Mayer, D. L., & Dobson, V. (1982). Visual acuity development in infants and young children, as assessed by operant preferential looking. *Vision Res, 22*(9), 1141-1151.

Mayer, D. L., Moore, B., & Robb, R. M. (1989). Assessment of vision and amblyopia by preferential looking tests after early surgery for unilateral congenital cataracts. *J Pediatr Ophthalmol Strabismus, 26*(2), 61-68.

McCollough, C. (1965). Color Adaptation of Edge-Detectors in the Human Visual System. *Science, 149*(3688), 1115-1116.

McCulloch, D. L., & Skarf, B. (1994). Pattern reversal visual evoked potentials following early treatment of unilateral, congenital cataract. *Arch Ophthalmol, 112*(4), 510-518.

McGee, A. W., Yang, Y., Fischer, Q. S., Daw, N. W., & Strittmatter, S. M. (2005). Experience-driven plasticity of visual cortex limited by myelin and Nogo receptor. *Science, 309*(5744), 2222-2226.

McKee, S. P., Levi, D. M., & Movshon, J. A. (2003). The pattern of visual deficits in amblyopia. *J Vis, 3*(5), 380-405.

Meng, M., & Tong, F. (2004). Can attention selectively bias bistable perception? Differences between binocular rivalry and ambiguous figures. *J Vis, 4*(7), 539-551.

Merabet, L. B., Hamilton, R., Schlaug, G., Swisher, J. D., Kiriakopoulos, E. T., Pitskel, N. B., et al. (2008). Rapid and reversible recruitment of early visual cortex for touch. *PLoS One, 3*(8), e3046.

Merabet, L. B., Swisher, J. D., McMains, S. A., Halko, M. A., Amedi, A., Pascual-Leone, A., et al. (2007). Combined activation and deactivation of visual cortex during tactile sensory processing. *J Neurophysiol, 97*(2), 1633-1641.

Meredith, M. A., Nemitz, J. W., & Stein, B. E. (1987). Determinants of multisensory integration in superior colliculus neurons. I. Temporal factors. *J Neurosci, 7*(10), 3215-3229.

Meredith, M. A., & Stein, B. E. (1983). Interactions among converging sensory inputs in the superior colliculus. *Science, 221*(4608), 389-391.

Meredith, M. A., & Stein, B. E. (1986). Spatial factors determine the activity of multisensory neurons in cat superior colliculus. *Brain Res, 365*(2), 350-354.

Meredith, M. A., & Stein, B. E. (1990). The visuotopic component of the multisensory map in the deep laminae of the cat superior colliculus. *J Neurosci, 10*(11), 3727-3742.

Meredith, M. A., & Stein, B. E. (1996). Spatial determinants of multisensory integration in cat superior colliculus neurons. *J Neurophysiol, 75*(5), 1843-1857.

Meyer, D. E., & Schvaneveldt, R. W. (1971). Facilitation in recognizing pairs of words: evidence of a dependence between retrieval operations. *J Exp Psychol, 90*(2), 227-234.

Miller, S. M., Hansell, N. K., Ngo, T. T., Liu, G. B., Pettigrew, J. D., Martin, N. G., et al. (2010). Genetic contribution to individual variation in binocular rivalry rate. *Proc Natl Acad Sci U S A, 107*(6), 2664-2668.

Miller, S. M., Liu, G. B., Ngo, T. T., Hooper, G., Riek, S., Carson, R. G., et al. (2000). Interhemispheric switching mediates perceptual rivalry. *Curr Biol, 10*(7), 383-392.

Mioche, L., & Perenin, M. T. (1986). Central and peripheral residual vision in humans with bilateral deprivation amblyopia. *Exp Brain Res, 62*(2), 259-272.

Mitchell, D. E., & Sengpiel, F. (2009). Neural mechanisms of recovery following early visual deprivation. *Philos Trans R Soc Lond B Biol Sci, 364*(1515), 383-398.

Mitchell, J. F., Stoner, G. R., & Reynolds, J. H. (2004). Object-based attention determines dominance in binocular rivalry. *Nature, 429*(6990), 410-413.

Mittmann, T., Luhmann, H. J., Schmidt-Kastner, R., Eysel, U. T., Weigel, H., & Heinemann, U. (1994). Lesion-induced transient suppression of inhibitory function in rat neocortex in vitro. *Neuroscience, 60*(4), 891-906.

Moradi, F., Koch, C., & Shimojo, S. (2005). Face adaptation depends on seeing the face. *Neuron, 45*(1), 169-175.

Morein-Zamir, S., Soto-Faraco, S., & Kingstone, A. (2003). Auditory capture of vision: examining temporal ventriloquism. *Brain Res Cogn Brain Res, 17*(1), 154-163.

Morishita, H., Miwa, J. M., Heintz, N., & Hensch, T. K. (2010). Lynx1, a cholinergic brake, limits plasticity in adult visual cortex. *Science, 330*(6008), 1238-1240.

Morrone, M. C., Burr, D. C., & Fiorentini, A. (1990). Development of contrast sensitivity and acuity of the infant colour system. *Proc Biol Sci, 242*(1304), 134-139.

Morrone, M. C., Burr, D. C., & Maffei, L. (1982). Functional implications of cross-orientation inhibition of cortical visual cells. I. Neurophysiological evidence. *Proc R Soc Lond B Biol Sci, 216*(1204), 335-354.

Moutoussis, K., Keliris, G., Kourtzi, Z., & Logothetis, N. (2005). A binocular rivalry study of motion perception in the human brain. *Vision Res, 45*(17), 2231-2243.

Moutoussis, K., & Zeki, S. (2002). The relationship between cortical activation and perception investigated with invisible stimuli. *Proc Natl Acad Sci U S A, 99*(14), 9527-9532.

Movshon, J. A., & Blakemore, C. (1973). Orientation specificity and spatial selectivity in human vision. *Perception, 2*(1), 53-60.

Movshon, J. A., & Lennie, P. (1979). Pattern-selective adaptation in visual cortical neurones. *Nature, 278*(5707), 850-852.

Mower, G. D. (1991). The effect of dark rearing on the time course of the critical period in cat visual cortex. *Brain Res Dev Brain Res, 58*(2), 151-158.

Mrsic-Flogel, T. D., Hofer, S. B., Ohki, K., Reid, R. C., Bonhoeffer, T., & Hubener, M. (2007). Homeostatic regulation of eye-specific responses in visual cortex during ocular dominance plasticity. *Neuron, 54*(6), 961-972.

Mueller, T. J., & Blake, R. (1989). A fresh look at the temporal dynamics of binocular rivalry. *Biol Cybern, 61*(3), 223-232.

Nachmias, J., & Sansbury, R. V. (1974). Letter: Grating contrast: discrimination may be better than detection. *Vision Res, 14*(10), 1039-1042.

Necker, L. A. (1832). Observation on some remarkable optical phaenomena seen in Switzerland; and an optical phaenomenon which occurs on viewing a figure of a crystal or geometrical solid. *London and Edinburgh Philosophical Magazine and Journal of Science, 1*(5), 329-337.

Newell, F. N., & Bulthoff, H. H. (2002). Categorical perception of familiar objects. *Cognition, 85*(2), 113-143.

Newell, F. N., Bulthoff, H. H., & Ernst, M. O. (2003). Cross-modal perception of actively explored objects. In S. e. a. O'Modhrain (Ed.), *Eurohaptics 2003 Conference Proceedings* (pp. 291-299).

Newsome, W. T., & Pare, E. B. (1988). A selective impairment of motion perception following lesions of the middle temporal visual area (MT). *J Neurosci, 8*(6), 2201-2211.

Nguyen, V. A., Freeman, A. W., & Alais, D. (2003). Increasing depth of binocular rivalry suppression along two visual pathways. *Vision Res, 43*(19), 2003-2008.

Noest, A. J., van Ee, R., Nijs, M. M., & van Wezel, R. J. (2007). Percept-choice sequences driven by interrupted ambiguous stimuli: a low-level neural model. *J Vis, 7*(8), 10.

O'Shea, R. P., & Crassini, B. (1981a). Interocular transfer of the motion after-effect is not reduced by binocular rivalry. *Vision Res, 21*(6), 801-804.

O'Shea, R. P., & Crassini, B. (1981b). The sensitivity of binocular rivalry suppression to changes in orientation assessed by reaction-time and forced-choice techniques. *Perception, 10*(3), 283-293.

Olson, C. R., & Freeman, R. D. (1980). Profile of the sensitive period for monocular deprivation in kittens. *Exp Brain Res, 39*(1), 17-21.

Ooi, T. L., & He, Z. J. (1999). Binocular rivalry and visual awareness: the role of attention. *Perception, 28*(5), 551-574.

Ooi, T. L., & Loop, M. S. (1994). Visual suppression and its effect upon color and luminance sensitivity. *Vision Res, 34*(22), 2997-3003.

Ostrovsky, Y., Andalman, A., & Sinha, P. (2006). Vision following extended congenital blindness. *Psychol Sci, 17*(12), 1009-1014.

Ostrovsky, Y., Meyers, E., Ganesh, S., Mathur, U., & Sinha, P. (2009). Visual parsing after recovery from blindness. *Psychol Sci, 20*(12), 1484-1491.

Paffen, C. L., & Alais, D. (2012). Attentional modulation of binocular rivalry. *Front Hum Neurosci, 5*, 105.

Paffen, C. L., Alais, D., & Verstraten, F. A. (2006). Attention speeds binocular rivalry. *Psychol Sci, 17*(9), 752-756.

Paffen, C. L., Hooge, I. T., Benjamins, J. S., & Hogendoorn, H. (2011). A search asymmetry for interocular conflict. *Atten Percept Psychophys, 73*(4), 1042-1053.

Paffen, C. L., Naber, M., & Verstraten, F. A. (2008). The spatial origin of a perceptual transition in binocular rivalry. *PLoS One, 3*(6), e2311.

Paffen, C. L., & Van der Stigchel, S. (2010). Shifting spatial attention makes you flip: Exogenous visual attention triggers perceptual alternations during binocular rivalry. *Atten Percept Psychophys, 72*(5), 1237-1243.

Pascual-Leone, A., Amedi, A., Fregni, F., & Merabet, L. B. (2005). The plastic human brain cortex. *Annu Rev Neurosci, 28*, 377-401.

Pasley, B. N., Mayes, L. C., & Schultz, R. T. (2004). Subcortical discrimination of unperceived objects during binocular rivalry. *Neuron, 42*(1), 163-172.

Pastukhov, A., & Braun, J. (2008). A short-term memory of multi-stable perception. *J Vis, 8*(13), 7 1-14.

Pavani, F., Spence, C., & Driver, J. (2000). Visual capture of touch: out-of-the-body experiences with rubber gloves. *Psychol Sci, 11*(5), 353-359.

Pearson, J., & Clifford, C. W. (2005a). Suppressed patterns alter vision during binocular rivalry. *Curr Biol, 15*(23), 2142-2148.

Pearson, J., & Clifford, C. W. (2005b). When your brain decides what you see: grouping across monocular, binocular, and stimulus rivalry. *Psychol Sci, 16*(7), 516-519.

Peckham, R. H. (1936). Eye movements during "retinal rivalry". *Am J Psychol, 48*, 43-63.

Pelli, D. G. (1987). The visual requirements of mobility. In G. C. Woo (Ed.), *Low vision: Principles and applications* (pp. 134-146). New York, NY: Springer Verlag.

Perez, G. M., Archer, S. M., & Artal, P. (2010). Optical characterization of Bangerter foils. *Invest Ophthalmol Vis Sci, 51*(1), 609-613.

Pham, T. A., Graham, S. J., Suzuki, S., Barco, A., Kandel, E. R., Gordon, B., et al. (2004). A semi-persistent adult ocular dominance plasticity in visual cortex is stabilized by activated CREB. *Learn Mem, 11*(6), 738-747.

Phillips, G. C., & Wilson, H. R. (1984). Orientation bandwidths of spatial mechanisms measured by masking. *J Opt Soc Am A, 1*(2), 226-232.

Pizzorusso, T., Medini, P., Berardi, N., Chierzi, S., Fawcett, J. W., & Maffei, L. (2002). Reactivation of ocular dominance plasticity in the adult visual cortex. *Science, 298*(5596), 1248-1251.

Polonsky, A., Blake, R., Braun, J., & Heeger, D. J. (2000). Neuronal activity in human primary visual cortex correlates with perception during binocular rivalry. *Nat Neurosci, 3*(11), 1153-1159.

Posner, M. I., & Dehaene, S. (1994). Attentional networks. *Trends Neurosci, 17*(2), 75-79.

Purpura, K., Kaplan, E., & Shapley, R. M. (1988). Background light and the contrast gain of primate P and M retinal ganglion cells. *Proc Natl Acad Sci U S A, 85*(12), 4534-4537.

Putignano, E., Lonetti, G., Cancedda, L., Ratto, G., Costa, M., Maffei, L., et al. (2007). Developmental downregulation of histone posttranslational modifications regulates visual cortical plasticity. *Neuron, 53*(5), 747-759.

Rahi, J. S., Logan, S., Borja, M. C., Timms, C., Russell-Eggitt, I., & Taylor, D. (2002). Prediction of improved vision in the amblyopic eye after visual loss in the non-amblyopic eye. *Lancet, 360*(9333), 621-622.

Raskin, L. A., Maital, S., & Bornstein, M. H. (1983). Perceptual categorization of color: a life-span study. *Psychol Res, 45*(2), 135-145.

Regal, D. M. (1981). Development of Critical flicker frequency in human infants. *Vision Res, 21*(4), 549-555.

Reynolds, J. H., & Chelazzi, L. (2004). Attentional modulation of visual processing. *Annu Rev Neurosci, 27*, 611-647.

Rockland, K. S., & Ojima, H. (2003). Multisensory convergence in calcarine visual areas in macaque monkey. *Int J Psychophysiol, 50*(1-2), 19-26.

Roder, B., Stock, O., Bien, S., Neville, H., & Rosler, F. (2002). Speech processing activates visual cortex in congenitally blind humans. *Eur J Neurosci, 16*(5), 930-936.

Roeber, U., & Schroger, E. (2004). Binocular rivalry is partly resolved at early processing stages with steady and with flickering presentation: a human event-related brain potential study. *Neurosci Lett, 371*(1), 51-55.

Rubin, E. (1915). *Synsoplevede Figurer. Studier i psykologisk Analyse*. Copenhagen: Gyldendal.

Sadato, N., Pascual-Leone, A., Grafman, J., Ibanez, V., Deiber, M. P., Dold, G., et al. (1996). Activation of the primary visual cortex by Braille reading in blind subjects. *Nature, 380*(6574), 526-528.

Saito, D. N., Okada, T., Honda, M., Yonekura, Y., & Sadato, N. (2006). Practice makes perfect: the neural substrates of tactile discrimination by Mah-Jong experts include the primary visual cortex. *BMC Neurosci, 7*, 79.

Sale, A., Maya Vetencourt, J. F., Medini, P., Cenni, M. C., Baroncelli, L., De Pasquale, R., et al. (2007). Environmental enrichment in adulthood promotes amblyopia recovery through a reduction of intracortical inhibition. *Nat Neurosci, 10*(6), 679-681.

Sasieni, L. (1978). The Frisby Stereotest. *The Optician, 176*(4544), 7-8, 10.

Sathian, K., Zangaladze, A., Hoffman, J. M., & Grafton, S. T. (1997). Feeling with the mind's eye. *Neuroreport, 8*(18), 3877-3881.

Sato, M., & Stryker, M. P. (2008). Distinctive features of adult ocular dominance plasticity. *J Neurosci, 28*(41), 10278-10286.

Sawtell, N. B., Frenkel, M. Y., Philpot, B. D., Nakazawa, K., Tonegawa, S., & Bear, M. F. (2003). NMDA receptor-dependent ocular dominance plasticity in adult visual cortex. *Neuron, 38*(6), 977-985.

Schiller, P. H., & Malpeli, J. G. (1978). Functional specificity of lateral geniculate nucleus laminae of the rhesus monkey. *J Neurophysiol, 41*(3), 788-797.

Schroeder, C. E., Lindsley, R. W., Specht, C., Marcovici, A., Smiley, J. F., & Javitt, D. C. (2001). Somatosensory input to auditory association cortex in the macaque monkey. *J Neurophysiol, 85*(3), 1322-1327.

Sekuler, R., Sekuler, A. B., & Lau, R. (1997). Sound alters visual motion perception. *Nature, 385*(6614), 308.

Sengpiel, F., Blakemore, C., Kind, P. C., & Harrad, R. (1994). Interocular suppression in the visual cortex of strabismic cats. *J Neurosci, 14*(11 Pt 2), 6855-6871.

Sengpiel, F., Stawinski, P., & Bonhoeffer, T. (1999). Influence of experience on orientation maps in cat visual cortex. *Nat Neurosci, 2*(8), 727-732.

Sereno, M. I., Dale, A. M., Reppas, J. B., Kwong, K. K., Belliveau, J. W., Brady, T. J., et al. (1995). Borders of multiple visual areas in humans revealed by functional magnetic resonance imaging. *Science, 268*(5212), 889-893.

Shams, L., Kamitani, Y., & Shimojo, S. (2000). Illusions. What you see is what you hear. *Nature, 408*(6814), 788.

Shannon, R. W., Patrick, C. J., Jiang, Y., Bernat, E., & He, S. (2011). Genes contribute to the switching dynamics of bistable perception. *J Vis, 11*(3).

Shapley, R., & Enroth-Cugell, C. (1984). Visuala daptation and retinal gain controls. *Prog Retin Res, 3*, 263-346.

Sheinberg, D. L., & Logothetis, N. K. (1997). The role of temporal cortical areas in perceptual organization. *Proc Natl Acad Sci U S A, 94*(7), 3408-3413.

Sheth, B. R., & Pham, T. (2008). How emotional arousal and valence influence access to awareness. *Vision Res, 48*(23-24), 2415-2424.

Shimojo, S., Kamitani, Y., & Nishida, S. (2001). Afterimage of perceptually filled-in surface. *Science, 293*(5535), 1677-1680.

Shimojo, S., & Nakayama, K. (1990). Real world occlusion constraints and binocular rivalry. *Vision Res, 30*(1), 69-80.

Silver, M. A., & Logothetis, N. K. (2007). Temporal frequency and contrast tagging bias the type of competition in interocular switch rivalry. *Vision Res, 47*(4), 532-543.

Simion, F., Regolin, L., & Bulf, H. (2008). A predisposition for biological motion in the newborn baby. *Proc Natl Acad Sci U S A, 105*(2), 809-813.

Singer, N., Eapen, M., Grillon, C., Ungerleider, L. G., & Hendler, T. (2012). Through the eyes of anxiety: Dissecting threat bias via emotional-binocular rivalry. *Emotion, 12*(5), 960-969.

Singer, W. (1988). Neuronal mechanisms of deprivation amblyopia. In G. Lennenstrand, G. K. Von Noorden & C. C. Campos (Eds.), *Strabismus and amblyopia: Experimental basis for advances in clinical management* (pp. 259-274). Ney Yoirk, NY: Plenum Press.

Sinha, P., & Held, R. (2012). Sight restoration. *F1000 Med Rep, 4*, 17.

Slater, A., Morison, V., & Somers, M. (1988). Orientation discrimination and cortical function in the human newborn. *Perception, 17*(5), 597-602.

Slutsky, D. A., & Recanzone, G. H. (2001). Temporal and spatial dependency of the ventriloquism effect. *Neuroreport, 12*(1), 7-10.

Smith, V. C., & Pokorny, J. (1975). Spectral sensitivity of the foveal cone photopigments between 400 and 500 nm. *Vision Res, 15*(2), 161-171.

Solomon, S. G., & Lennie, P. (2005). Chromatic gain controls in visual cortical neurons. *J Neurosci, 25*(19), 4779-4792.

Solomon, S. G., Peirce, J. W., Dhruv, N. T., & Lennie, P. (2004). Profound contrast adaptation early in the visual pathway. *Neuron, 42*(1), 155-162.

Spering, M., Pomplun, M., & Carrasco, M. (2009). Differential effects of suppressed visual motion information on perception and action during binocular rivalry flash suppression. *J Vis, 9*(8), 285, 285a, http://journalofvision.org/289/288/285/.

Srinivasan, R., & Petrovic, S. (2006). MEG phase follows conscious perception during binocular rivalry induced by visual stream segregation. *Cereb Cortex, 16*(5), 597-608.

Srinivasan, R., Russell, D. P., Edelman, G. M., & Tononi, G. (1999). Increased synchronization of neuromagnetic responses during conscious perception. *J Neurosci, 19*(13), 5435-5448.

Stanford, T. R., Quessy, S., & Stein, B. E. (2005). Evaluating the operations underlying multisensory integration in the cat superior colliculus. *J Neurosci, 25*(28), 6499-6508.

Stanley, J., Carter, O., & Forte, J. (2011). Color and luminance influence, but can not explain, binocular rivalry onset bias. *PLoS One, 6*(5), e18978.

Stanley, J., Forte, J. D., Cavanagh, P., & Carter, O. (2012). Onset rivalry: the initial dominance phase is independent of ongoing perceptual alternations. *Front Hum Neurosci, 5*, 140.

Stein, B. E., & Stanford, T. R. (2008). Multisensory integration: current issues from the perspective of the single neuron. *Nat Rev Neurosci, 9*(4), 255-266.

Stein, B. E., & Wallace, M. T. (1996). Comparisons of cross-modality integration in midbrain and cortex. *Prog Brain Res, 112*, 289-299.

Stein, T., & Sterzer, P. (2012). Not just another face in the crowd: Detecting emotional schematic faces during continuous flash suppression. *Emotion, 12*(5), 988-996.

Sterzer, P., Hilgenfeldt, T., Freudenberg, P., Bermpohl, F., & Adli, M. (2011). Access of emotional information to visual awareness in patients with major depressive disorder. *Psychol Med, 41*(8), 1615-1624.

Sterzer, P., Jalkanen, L., & Rees, G. (2009). Electromagnetic responses to invisible face stimuli during binocular suppression. *Neuroimage, 46*(3), 803-808.

Sterzer, P., & Rees, G. (2008). A neural basis for percept stabilization in binocular rivalry. *J Cogn Neurosci, 20*(3), 389-399.

Stevenson, R. A., & James, T. W. (2009). Audiovisual integration in human superior temporal sulcus: Inverse effectiveness and the neural processing of speech and object recognition. *Neuroimage, 44*(3), 1210-1223.

Stewart, C. E., Moseley, M. J., Stephens, D. A., & Fielder, A. R. (2004). Treatment dose-response in amblyopia therapy: the Monitored Occlusion Treatment of Amblyopia Study (MOTAS). *Invest Ophthalmol Vis Sci, 45*(9), 3048-3054.

Stiles, J. (2000). Neural plasticity and cognitive development. *Dev Neuropsychol, 18*(2), 237-272.

Stuit, S. M., Paffen, C. L., van der Smagt, M. J., & Verstraten, F. A. (2011). Suppressed images selectively affect the dominant percept during binocular rivalry. *J Vis, 11*(10).

Tagawa, Y., Kanold, P. O., Majdan, M., & Shatz, C. J. (2005). Multiple periods of functional ocular dominance plasticity in mouse visual cortex. *Nat Neurosci, 8*(3), 380-388.

Tanaka, S., Ribot, J., Imamura, K., & Tani, T. (2006). Orientation-restricted continuous visual exposure induces marked reorganization of orientation maps in early life. *Neuroimage, 30*(2), 462-477.

Thompson, D. A., Moller, H., Russell-Eggitt, I., & Kriss, A. (1996). Visual acuity in unilateral cataract. *Br J Ophthalmol, 80*(9), 794-798.

Tong, F. (2005). Investigations of the Neural Basis of Binocular Rivalry. In D. Alais & R. Blake (Eds.), *Binocular Rivalry* (A Bradford book ed., pp. 63-80). Cambridge, Massachusetts: The MIT Press.

Tong, F., & Engel, S. A. (2001). Interocular rivalry revealed in the human cortical blind-spot representation. *Nature, 411*(6834), 195-199.

Tong, F., Meng, M., & Blake, R. (2006). Neural bases of binocular rivalry. *Trends Cogn Sci, 10*(11), 502-511.

Tong, F., Nakayama, K., Vaughan, J. T., & Kanwisher, N. (1998). Binocular rivalry and visual awareness in human extrastriate cortex. *Neuron, 21*(4), 753-759.

Tononi, G., Srinivasan, R., Russell, D. P., & Edelman, G. M. (1998). Investigating neural correlates of conscious perception by frequency-tagged neuromagnetic responses. *Proc Natl Acad Sci U S A, 95*(6), 3198-3203.

Treisman, A. M., & Gelade, G. (1980). A feature-integration theory of attention. *Cogn Psychol, 12*(1), 97-136.

Tsuchiya, N., & Koch, C. (2005). Continuous flash suppression reduces negative afterimages. *Nat Neurosci, 8*(8), 1096-1101.

Tsuchiya, N., Koch, C., Gilroy, L. A., & Blake, R. (2006). Depth of interocular suppression associated with continuous flash suppression, flash suppression, and binocular rivalry. *J Vis, 6*(10), 1068-1078.

Tsuchiya, N., Moradi, F., Felsen, C., Yamazaki, M., & Adolphs, R. (2009). Intact rapid detection of fearful faces in the absence of the amygdala. *Nat Neurosci, 12*(10), 1224-1225.

Tulving, E., & Schacter, D. L. (1990). Priming and human memory systems. *Science, 247*(4940), 301-306.

Tytla, M. E., Maurer, D., Lewis, T. L., & Brent, H. P. (1988). Contrast sensitivity in children trated for congenital cataract. *Clinical Vision Sciences, 2*, 251-264.

Ungerleider, L. G., & Desimone, R. (1986). Cortical connections of visual area MT in the macaque. *J Comp Neurol, 248*(2), 190-222.

Ungerleider, L. G., Galkin, T. W., & Mishkin, M. (1983). Visuotopic organization of projections from striate cortex to inferior and lateral pulvinar in rhesus monkey. *J Comp Neurol, 217*(2), 137-157.

Vaegan, & Taylor, D. (1979). Critical period for deprivation amblyopia in children. *Trans Ophthalmol Soc U K, 99*(3), 432-439.

van Atteveldt, N. M., Formisano, E., Blomert, L., & Goebel, R. (2007). The effect of temporal asynchrony on the multisensory integration of letters and speech sounds. *Cereb Cortex, 17*(4), 962-974.

van Dam, L. C., & van Ee, R. (2006). The role of saccades in exerting voluntary control in perceptual and binocular rivalry. *Vision Res, 46*(6-7), 787-799.

van der Zwan, R., & Wenderoth, P. (1994). Psychophysical evidence for area V2 involvement in the reduction of subjective contour tilt aftereffects by binocular rivalry. *Vis Neurosci, 11*(4), 823-830.

van der Zwan, R., Wenderoth, P., & Alais, D. (1993). Reduction of a pattern-induced motion aftereffect by binocular rivalry suggests the involvement of extrastriate mechanisms. *Vis Neurosci, 10*(4), 703-709.

van Ee, R. (2005). Dynamics of perceptual bi-stability for stereoscopic slant rivalry and a comparison with grating, house-face, and Necker cube rivalry. *Vision Res, 45*(1), 29-40.

van Ee, R. (2009). Stochastic variations in sensory awareness are driven by noisy neuronal adaptation: evidence from serial correlations in perceptual bistability. *J Opt Soc Am A Opt Image Sci Vis, 26*(12), 2612-2622.

van Ee, R., Noest, A. J., Brascamp, J. W., & van den Berg, A. V. (2006). Attentional control over either of the two competing percepts of ambiguous stimuli revealed by a two-parameter analysis: means do not make the difference. *Vision Res, 46*(19), 3129-3141.

van Ee, R., van Boxtel, J. J., Parker, A. L., & Alais, D. (2009). Multisensory congruency as a mechanism for attentional control over perceptual selection. *J Neurosci, 29*(37), 11641-11649.

van Ee, R., van Dam, L. C., & Brouwer, G. J. (2005). Voluntary control and the dynamics of perceptual bi-stability. *Vision Res, 45*(1), 41-55.

Vasconcelos, N., Pantoja, J., Belchior, H., Caixeta, F. V., Faber, J., Freire, M. A., et al. (2011). Cross-modal responses in the primary visual cortex encode complex objects and correlate with tactile discrimination. *Proc Natl Acad Sci U S A, 108*(37), 15408-15413.

Viviani, P., Binda, P., & Borsato, T. (2007). Categorical perception of newly learned faces. *Vis Cognition, 15*(4), 420-467.

von der Malsburg, C. (1999). The what and why of binding: the modeler's perspective. *Neuron, 24*(1), 95-104, 111-125.

Wade, N. J., de Weert, C. M., & Swanston, M. T. (1984). Binocular rivalry with moving patterns. *Percept Psychophys, 35*(2), 111-122.

Wade, N. J., & Wenderoth, P. (1978). The influence of colour and contour rivalry on the magnitude of the tilt after-effect. *Vision Res, 18*(7), 827-835.

Wales, R., & Fox, R. (1970). Increment detection thresholds during binocular rivalry suppression. *Percept Psychophys, 8*, 90-94.

Walker, P., & Powell, D. J. (1979). The sensitivity of binocular rivalry to changes in the nondominant stimulus. *Vision Res, 19*(3), 247-249.

Wallace, M. T., Meredith, M. A., & Stein, B. E. (1992). Integration of multiple sensory modalities in cat cortex. *Exp Brain Res, 91*(3), 484-488.

Wallace, M. T., Roberson, G. E., Hairston, W. D., Stein, B. E., Vaughan, J. W., & Schirillo, J. A. (2004). Unifying multisensory signals across time and space. *Exp Brain Res, 158*(2), 252-258.

Wark, B., Fairhall, A., & Rieke, F. (2009). Timescales of inference in visual adaptation. *Neuron, 61*(5), 750-761.

Weakley, D. R., Jr. (2001). The association between nonstrabismic anisometropia, amblyopia, and subnormal binocularity. *Ophthalmology, 108*(1), 163-171.

Webber, A. L., & Wood, J. (2005). Amblyopia: prevalence, natural history, functional effects and treatment. *Clin Exp Optom, 88*(6), 365-375.

Welch, R. B., & Warren, D. H. (1980). Immediate perceptual response to intersensory discrepancy. *Psychol Bull, 88*(3), 638-667.

Wheatstone, C. (1838). Contributions to the physiology vision - Part first: on some remarkable, and hitherto unobserved, phenomena of binocular vision. *Philos Trans R Soc Lond B Biol Sci, 128*, 371-394.

Whittle, P. (1965). Binocular rivalry and the contrast at contours. *Q. J. Exp. Psychol, 17*(217-226).

Wiesel, T. N., & Hubel, D. H. (1963a). Effects of Visual Deprivation on Morphology and Physiology of Cells in the Cats Lateral Geniculate Body. *J Neurophysiol, 26*, 978-993.

Wiesel, T. N., & Hubel, D. H. (1963b). Single-Cell Responses in Striate Cortex of Kittens Deprived of Vision in One Eye. *J Neurophysiol, 26*, 1003-1017.

Wiesel, T. N., & Hubel, D. H. (1965a). Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. *J Neurophysiol, 28*(6), 1029-1040.

Wiesel, T. N., & Hubel, D. H. (1965b). Extent of recovery from the effects of visual deprivation in kittens. *J Neurophysiol, 28*(6), 1060-1072.

Wiesenfelder, H., & Blake, R. (1990). The neural site of binocular rivalry relative to the analysis of motion in the human visual system. *J Neurosci, 10*(12), 3880-3888.

Williams, M. A., Morris, A. P., McGlone, F., Abbott, D. F., & Mattingley, J. B. (2004). Amygdala responses to fearful and happy facial expressions under conditions of binocular suppression. *J Neurosci, 24*(12), 2898-2904.

Wilson, H. R. (1999). Non-fourier cortical process in texture, form and motion perception. In P. S. Ulinski, E. G. Jones & A. Peters (Eds.), *Cerebral Cortex. Models of Cortical Circuit.* (Vol. 13, pp. 445-477). New York (NY): Plenum Press.

Wilson, H. R. (2003). Computational evidence for a rivalry hierarchy in vision. *Proc Natl Acad Sci U S A, 100*(24), 14499-14503.

Wilson, H. R., Blake, R., & Lee, S. H. (2001). Dynamics of travelling waves in visual perception. *Nature, 412*(6850), 907-910.

Witten, I. B., & Knudsen, E. I. (2005). Why seeing is believing: merging auditory and visual worlds. *Neuron, 48*(3), 489-496.

Wolfe, J. M. (1984). Reversing ocular dominance and suppression in a single flash. *Vision Res, 24*(5), 471-478.

Wright, R. D., & Frenzel, S. L. (2008). *Orienting of Attention*. Oxford: Oxford University Press.

Wunderlich, K., Schneider, K. A., & Kastner, S. (2005). Neural correlates of binocular rivalry in the human lateral geniculate nucleus. *Nat Neurosci, 8*(11), 1595-1602.

Xu, J. P., He, Z. J., & Ooi, T. L. (2010). Effectively reducing sensory eye dominance with a push-pull perceptual learning protocol. *Curr Biol, 20*(20), 1864-1868.

Yang, E., Zald, D. H., & Blake, R. (2007). Fearful expressions gain preferential access to awareness during continuous flash suppression. *Emotion, 7*(4), 882-886.

Zangaladze, A., Epstein, C. M., Grafton, S. T., & Sathian, K. (1999). Involvement of visual cortex in tactile discrimination of orientation. *Nature, 401*(6753), 587-590.

Zenger-Landolt, B., & Heeger, D. J. (2003). Response suppression in v1 agrees with psychophysics of surround masking. *J Neurosci, 23*(17), 6884-6893.

Zhang, P., Bao, M., Kwon, M., He, S., & Engel, S. A. (2009). Effects of orientation-specific visual deprivation induced with altered reality. *Curr Biol, 19*(22), 1956-1960.

Zhang, P., Jamison, K., Engel, S., He, B., & He, S. (2011). Binocular rivalry requires visual attention. *Neuron, 71*(2), 362-369.

Zimba, L. D., & Blake, R. (1983). Binocular rivalry and semantic processing: out of sight, out of mind. *J Exp Psychol Hum Percept Perform, 9*(5), 807-815.

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