CORTICAL MECHANISMS OF VISUAL ATTENTION IN TYPICALLY DEVELOPING INFANTS AND ADULTS

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Declaration

I, Louisa Valerie Kulke confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

This thesis used a combined methodology of on-line eye tracking and high density EEG to study neural mechanisms of attention development in infants and adults. The extensively studied Fixation Shift Paradigm (FSP) measures the ability to shift attention between two stimuli (competition) or towards one single visible stimulus (non-competition) which improves during infancy. The novel method here overcame a number of methodological challenges to measure event-rated potentials during overt shifts of attention in competition and non-competition conditions. An experiment used eye tracking to test infants between 1 and 8 months on the FSP, establishing that this automated measure is suitable for non-verbal populations and adds precision to the developmental trends previously reported.

An experiment successfully combined eye tracking and EEG to record patterns of brain activity during covert and overt attention shifts in adults. It found that neural mechanisms previously studied in covert attention shifts are similar to those in overt shifts, but differ in a frontal positivity, possibly reflecting saccade inhibition. Combined eye tracking and EEG with the original FSP showed that similar cortical mechanisms are involved in attention shifts under competition and non-competition conditions but that occipital response latencies differ at an early stage, reflecting the behavioural pattern of shorter latencies in non-competition conditions. Parallel measurements during infancy showed that the lateralisation of frontal brain responses coincides with developmental improvements in the ability to shift attention.

In conclusion, the work demonstrates that, with suitable precautions taken to avoid artefacts, eye tracking and EEG can be successfully combined to monitor group-level brain mechanisms during overt attention shifts. Neurodevelopmental changes have been identified that underpin the increasing efficiency of neural attention pathways during infancy, and increased automation of responses from reliance on frontal pathways in infancy to occipital pathways in adulthood.

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Dr John Wattam-Bell was my primary supervisor until he sadly passed away during the second year of my PhD. He inspired me and helped me pursue my passion for science. It was a pleasure and honour to work with John.

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This thesis is dedicated to Dr John Wattam-Bell.

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List of abbreviations

ADHD	Attention deficit hyperactivity disorder
DTI	Diffusion tensor imaging
EEG	Electroencephalography
ERP	Event-related potential
F	Frontal
FA	Fractional anisotropy
FC	Fronto-central
FEF	Frontal eye fields
FMRI	Functional magnetic resonance imaging
FSP	Fixation Shift Paradigm
HIE	Hypoxic-ischaemic encephalopathy
IP	Intraparietal sulcus
IS	Interactive specialisation
MD	Medio dorsal thalamus
MRI	Magnetic resonance imaging
PC	Parietal cortex
PET	Positron emission topography
PPC	Posterior parietal cortex
SC	Superior colliculus
SLF	Superior longitudinal fascicle
SN	Substantia nigra
SSVEP	Steady-state visually evoked potential
TOJ	Temporoparietal junction
V1	Primary visual cortex
VC	Visual cortex
VEP/ VERP	Visually evoked potential
VFC	Ventral frontal cortex

Introduction

Attention is a set of cognitive processes that is the basis for survival and development, allowing us to process cars approaching us at a road and reacting to them by refraining from crossing, or allowing children to pay attention to relevant subject matters in school while ignoring their chatting classmates. An early development of the ability to shift attention to relevant objects is therefore crucial for future development. However, the mechanisms underlying this development are still under debate. This thesis aims to investigate brain mechanisms of attention in adults and the development of these mechanisms during infancy. A novel combination of eye-tracking and EEG was used, making it possible to monitor brain activation during natural overt shifts of attention. This allows a detailed investigation of the time course of brain responses from different areas of the scalp, which provides new insights to the mechanisms involved in attention in both adults and infants. The ability to disengage attention has been reported to be limited in early infancy and is impaired in a number of different disorders. The research reported here can define a baseline for typical development, using eye tracking technology, which can be used to map the differences in atypically developing populations. The first part of this thesis (Chapter 2 to 4) describes how the novel methodology combining eye-tracking and EEG was developed, tested on infant and adult populations, the accuracy was determined and how the results from these studies were linked to previous research. In the second part (Chapter 5 to 7) the method is used to investigate changes in the ability to disengage and shift attention with age (*Figure 0.1*).

Chapter 1 summarises the current literature on attention, the development of the ability to shift attention and attention-related brain structures and networks in infants and adults that form a basis for the thesis. It shows that neural studies on overt attention shifts are rare and that there is currently still a lack of research supporting models of the development of the ability to overtly shift attention from infancy to adulthood. Therefore, the main aims of this thesis were to (1.) develop a method to measure neural mechanisms of overt attention shifts (Chapters 2 to 4) and to (2.) use this method to investigate the development of brain responses during overt attention shifts in infants and adults (Chapter 5 and 6).

Chapter 2 goes into more technical detail on the methods used in this thesis, providing a critical evaluation of the use of eye-tracking and electroencephalography

(EEG) for this thesis, summarising the common methods used in the different studies, reviewing the time course and localisation of event-related potential (ERP) components that were expected to occur and reasoning why specific areas and time-windows of interest were extracted.

Chapter 3 describes a program that was written to automate the Fixation Shift Paradigm (FSP) and its testing of infants. Previously this paradigm has been conducted by adult observers who judged infants' saccades using a forced choice preferential looking procedure or by frame-by-frame video analysis. In this study, it was combined with eye-tracking to allow a temporally accurate and time efficient measure of attention shifts.

Chapter 4 describes results of combined eye-tracking and EEG to simultaneously record saccades and brain responses in adults for both covert and overt attention shifts. Most previous studies instructed their participants (adults) to attend covertly in a given location, inhibiting an eye movement to that location, and simultaneously detect specific stimuli while inhibiting eye-movements. Chapter 4 aimed to create a bridge between previous covert attention studies and the overt attention shifts measured in this thesis. Adult subjects completed tasks similar to the FSP, during which they either had to manually respond to a peripheral target while maintaining central fixation (covert shift) or make a saccade towards a peripheral stimulus (overt shift).

Chapter 5 combined the Fixation Shift Paradigm with eye-tracking and EEG to study differences between shifts involving disengagement or no disengagement in adults. To investigate whether differences between conditions in the EEG recorded are only responses to the offset of the central stimulus, a second study was conducted to subtract the offset response from the raw wave.

Chapter 6 uses the newly established method combining the FSP with eye-tracking and EEG to test infants between 1 and 8 months of age.

Chapter 7 summarises all findings, draws conclusions about cortical mechanisms of visual attention in adults and infants and suggests future studies and analyses using this paradigm.

The appendix summarises a number of pilot experiments which are related to studies in the thesis.

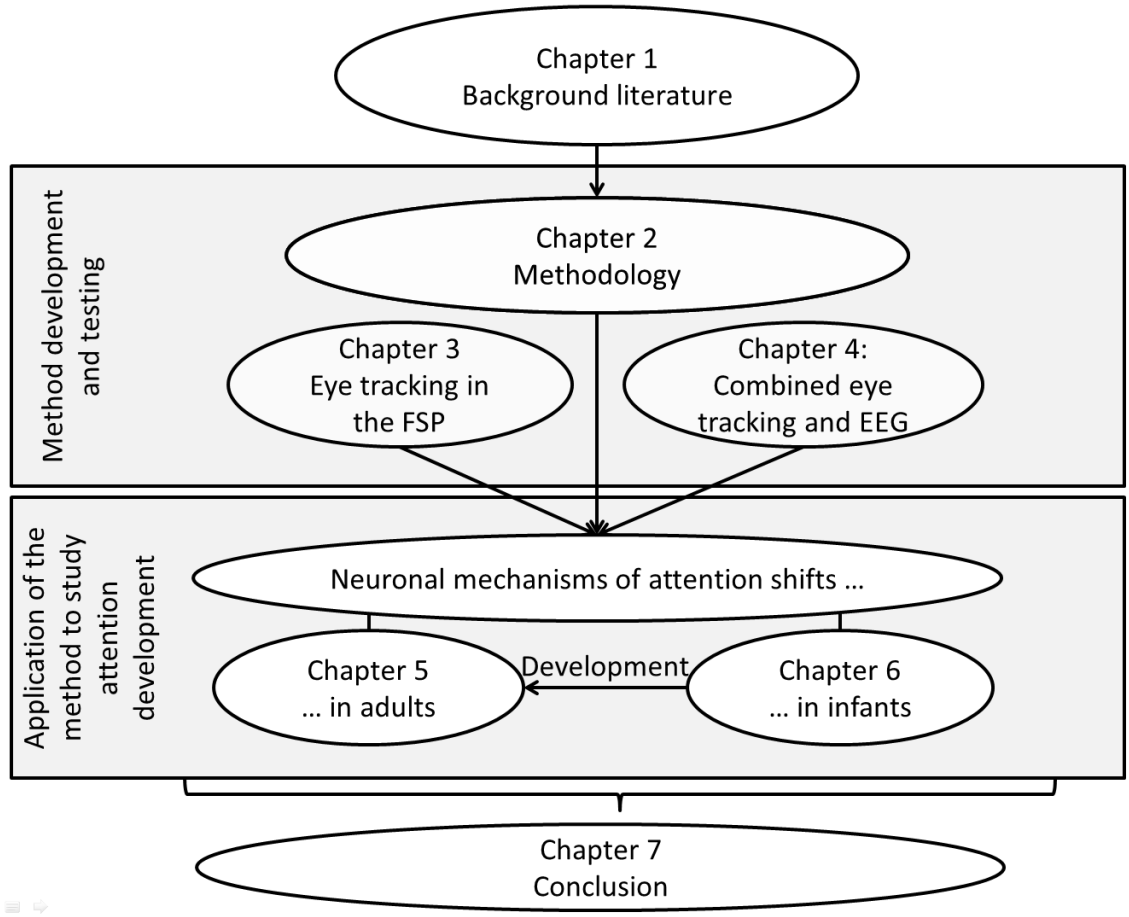


Figure 0.1. Structure of the thesis. This thesis develops a new method of combined eye tracking and EEG (Chapters 2 to 4) and then uses it to investigate neural mechanisms of attention shifts in adults and infants (Chapters 5 and 6).

Chapter 1 Literature Background

The introduction outlined that this thesis investigates the neural mechanisms of attention in infants and adults by combining eye-tracking and EEG. This chapter will provide a summary of background literature, first describing how attention is defined and how it can be studied in adults and infants, then describing the brain mechanisms involved in attention and finally discussing how they are thought to develop with age.

1.1 Attention

Attention can be considered as a "selection for action" (Allport, 1989), allowing us to select relevant objects for action, while inhibiting irrelevant objects (*Figure 1.1*). This ability plays an important role in everyday life, for example for being able to concentrate on learning matters in school, selecting to look at the teacher who is writing examples at the board instead of selecting to look out of the window at the noisy children on the playground. Concentrating on relevant events allows children to learn from them, which is crucial for future development. Important milestones of attention development are achieved early in life during infancy (cf. Colombo, 2001; Hood & Atkinson, 1993), serving as an important basis for different facets of attention that are normally present in adulthood.

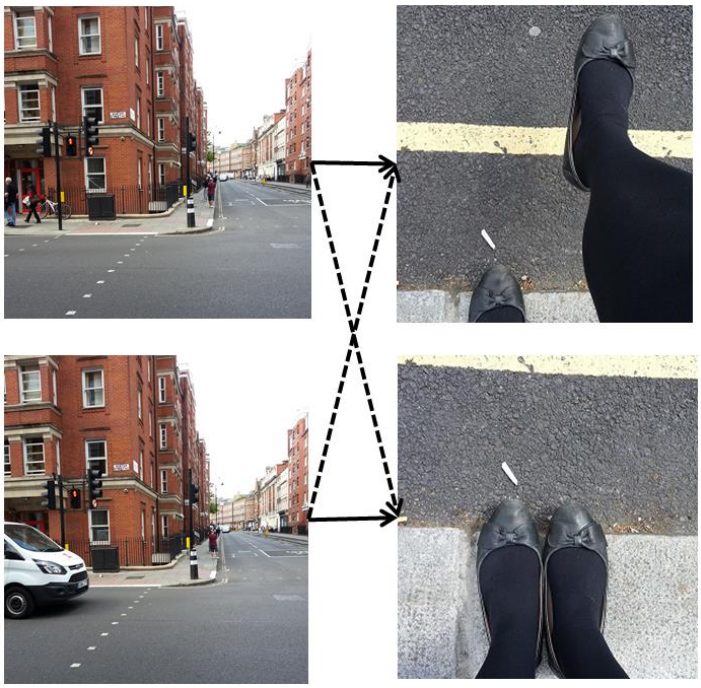


Figure 1.1. Attention as a "selection for action". Attention to a scene or stimulus can facilitate responses to this scene. If attention is directed at a car approaching (bottom scene), the selected action should be to stop, whereas if attention falls on an empty road (top scene) the action would be to walk. However, the selected action depends on which object attention is directed to (e.g. if it is directed to the red traffic light, one would always stop (though not usually in London), whereas if it is directed to cars one may choose to walk).

One aspect of attention is the ability to direct processing capacity to a spatial location or object (cf. Colombo, 2001; Posner & Boies, 1971), which has been termed "orienting of attention" (e.g. Posner & Rothbart, 2007). Usually orienting of attention to an object is accompanied with an eye-movement towards it, which would be the selected action (e.g. Posner, Cohen, & Rafal, 1982). However, attention can also be covert, meaning that processing capacity is shifted towards an object without an eye-movement (Colby, Duhamel, & Goldberg, 1996; Mountcastle, 1978; Posner et al., 1982; Posner & Petersen, 1989). This covert shift reveals itself in shorter reaction times (e.g. Colegate, Hoffman, & Eriksen, 1973; Eriksen & Hoffman, 1973; Luck, Hillyard, Mouloua, & Hawkins, 1996; Posner, 1980; Posner et al., 1982; Prinzmetal, McCool, & Park, 2005), lower error rates (Luck et al., 1996; Posner et al., 1982), a higher probability of detecting near-threshold events (Bashinski & Bacharach, 1980) or changes in neural activity induced by the target (e.g. Colby et al., 1996; Goldberg & Wurtz, 1972b) compared to unattended stimuli. Attentional enhancements of objects

have first been suggested to occur on an early perceptual level (Broadbent, 1958; Lachter, Forster, & Ruthruff, 2004), while later accounts suggest that attention only affects late response selection (Deutsch & Deutsch, 1963). The stage at which attention starts to affect processing may depend on task difficulty (perceptual load) of an attentional task (Lavie, 2006). In summary, selective attention can facilitate various reactions. The extent of this facilitation effect can vary (Prinzmetal et al., 2005), depending on whether attention is directed voluntarily, controlled by the observer (*endogenous/ top-down attention*) or automatically, without voluntary control (*exogenous/ bottom-up attention*) (e.g. Carrasco & Yeshurun, 2009; Posner, 1980). Bottom-up orienting of attention is measured in this thesis to map the development of the ability to shift attention and the brain mechanisms that are involved in it.

1.2 Attention tasks in adults

Several behavioural tasks have been developed to investigate different facets or components of attention in adults (cf. Posner & Boies, 1971; Posner & Snyder, 2004 for an overview). A particularly well-known and highly cited paradigm is the Spatial Cueing Task developed by Posner (1980), which involves shifts of attention between objects in different spatial locations. Subjects are instructed either to covertly shift their attention towards a target and react to it or to move their eyes overtly towards it. In different versions of the paradigm the target is preceded by a cue that directs attention, leading to facilitated reactions and increased neural responses to the target (Colby et al., 1996; Goldberg & Wurtz, 1972b; Posner, 1980; Posner et al., 1982). The paradigm has been used to investigate differences between endogenous and exogenous orienting (e.g. H. J. Müller & Rabbitt, 1989), differences between healthy adults and patient groups (e.g. Posner et al., 1982; Posner, Walker, Friedrich, & Rafal, 1984) and brain mechanisms involved in attention (e.g. Corbetta, Kincade, Ollinger, McAvoy, & Shulman, 2000). In summary, Posner's cueing paradigm is an extensively studied attention task that can provide insights to the mechanisms of orienting of attention.

1.3 Attention development in infants

1.3.1 Measuring attention in infants

Adult attention tasks, like the Posner Paradigm usually rely on verbal instructions, making them unsuitable for non-verbal populations like infants or

individuals with communications difficulties. Most tests of cognitive function can only be used from school age on, as they are based on verbal instructions, meaning that treatment outcomes cannot be investigated before this age (e.g. Lucas, Morley, & Cole, 1998). They therefore need to be modified for use in younger populations. As it is not possible to verbally instruct infants to covertly shift their attention, only few indirect measures of covert attention are possible in infants (see M. H. Johnson, 2002 for a review). However, two well-established behavioural methods to examine overt shifts of attention in young infants, are the Fixation Shift Paradigm (FSP, e.g. Atkinson & Braddick, 2012 (review); Atkinson, Hood, Braddick, & Wattam-Bell, 1988; Atkinson, Hood, Wattam-Bell, & Braddick, 1992; Butcher, Kalverboer, & Geuze, 2000; Hood & Atkinson, 1993) and the Gap Paradigm (e.g. Colombo, 2001; Elsabbagh et al., 2013; Elsabbagh et al., 2009; Farroni, Simion, Umiltà, & Barba, 1999; M. H. Johnson, Posner, & Rothbart, 1991; Matsuzawa & Shimojo, 1997). In the FSP infants are shown one stimulus centred on a screen for a short period of time. A second one is then presented in another location - either while the first stimulus is still present (competition condition), or immediately after the first stimulus disappears (non-competition condition). The gap paradigm introduces an additional condition in which the second stimulus appears after the first stimulus has been turned off for a certain time (gap condition, e.g. FSP: Atkinson & Braddick, 1985; Colombo, 2001; Hood & Atkinson, 1993; gap paradigm: Matsuzawa & Shimojo, 1997), see *Figure 1.2*.

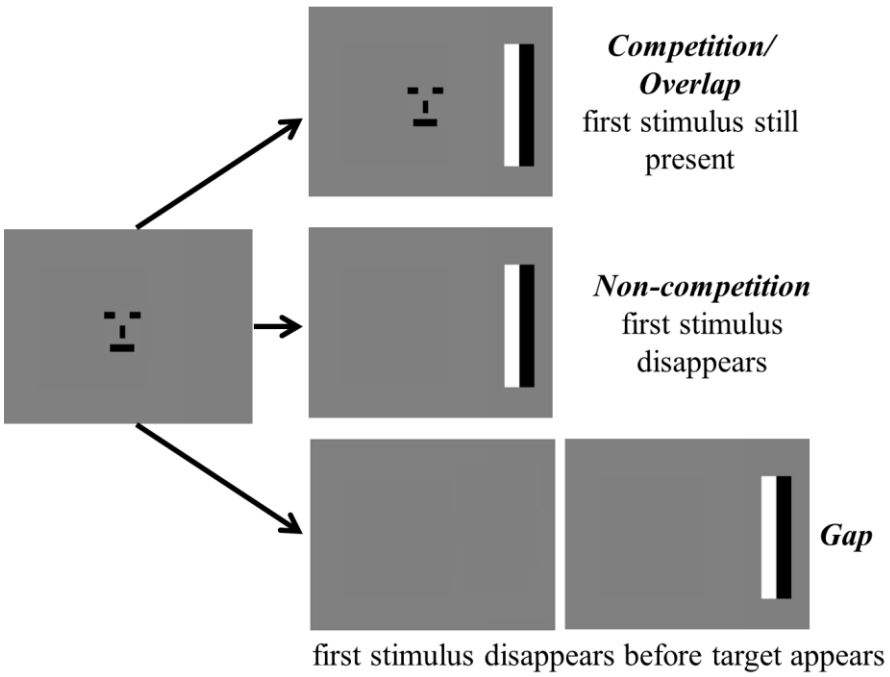


Figure 1.2. Conditions used in the Fixation Shift Paradigm and Gap-Overlap Paradigm. A central stimulus appears (left) and when the subject fixates on it, a second stimulus appears, either while the first one is still visible (competition/ overlap condition, top), while the first stimulus disappears (non-competition, middle) or after a temporal gap (gap, bottom).

In both paradigms the time until the first saccade towards the peripheral stimulus is measured to investigate the infants' ability to switch attention in the different conditions. Saccade latencies have been found to differ between conditions, being lowest in the gap-condition, intermediate in the non-competition condition and highest when disengagement is required in the competition condition (e.g. Atkinson & Braddick, 1985; Colombo, 2001; Hood & Atkinson, 1993). Comparing competition and non-competition conditions, young infants in the first two to four months of life are slow at switching attention to the peripheral target if the competing central stimulus stays visible, and sometimes do not disengage attention and shift their gaze from the central stimulus at all. However, they are able to relatively quickly shift attention when the central stimulus disappears before the peripheral stimulus appears (Atkinson & Braddick, 1985; Atkinson et al., 1988; Atkinson et al., 1992; P. Harris & MacFarlane, 1974; Hood & Atkinson, 1993; M. H. Johnson et al., 1991). The main improvements happen within the first 4 months of life, particularly between 9 and 16 weeks of age, but changes still occur until later during infancy (Butcher et al., 2000). Several other skills related to orienting of attention also develop around 4 months of life (M. H. Johnson et

al., 1991), indicating that this is an important age for attention development. When younger infants become stuck on a stimulus and are unable to inhibit or disengage their attention and look elsewhere, this has been called "sticky fixations", rarely occurring beyond the first two months of life (e.g. Atkinson & Braddick, 1985; Hood, 1995; Hood, Atkinson, & Braddick, 1998; M. H. Johnson et al., 1991). In summary, infants' performance under competition improves with age.

Shifting attention under competition involves three distinct steps (*Figure 1.3*): disengaging from the current stimulus, followed by a shift of attention and finally an engagement with the new target (Colombo, 2001; Hood & Atkinson, 1993; Posner & Cohen, 1984). As shifting and engaging of attention in the non-competition condition are already operational in young infants, the disengagement process seems to be the driving force for slower saccades and sticky fixations under competition. Saccades in non-competition conditions seem to involve subcortical structures, while disengagement requires cortical control of subcortical mechanisms, as infants who had one of their brain hemispheres surgically removed (hemispherectomised infants) can shift attention in non-competition conditions but show impairments under competition (Braddick et al., 1992). On the whole, early attentional mechanisms allow infants to shift gaze towards salient targets and the ability to actively control shifts between different stimuli is improving within the first months of life (Bronson, 1974).

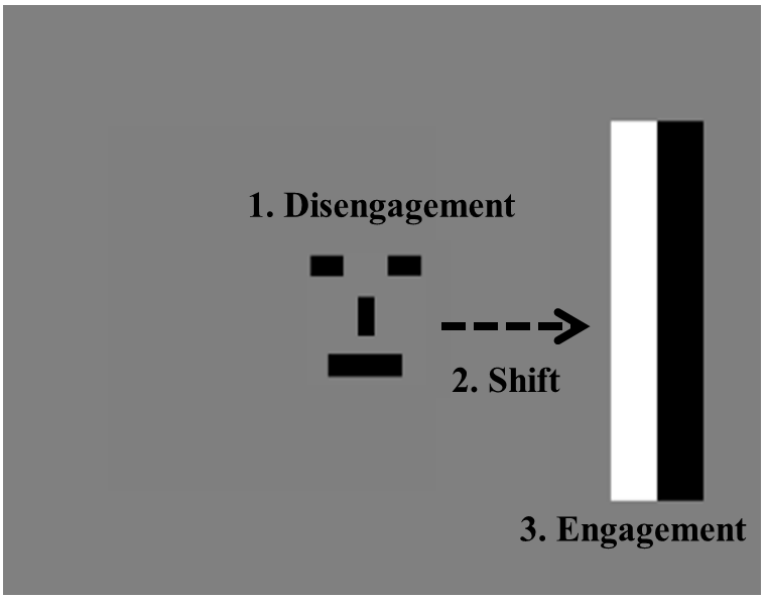


Figure 1.3. Three distinct steps involved in attention shifts: (1.) Disengagement from the central stimulus, (2.) a shift of processing capacity towards the new target and (3.) an engagement of attention with the target.

The attentional visual system develops rapidly within the first year of life and not only the ability to disengage from a stimulus, but also the accuracy of saccades towards a subsequent target improves with age (Aslin & Salapatek, 1975), possibly because the physical features of the visual system are dynamically changing and developing (e.g. cone receptors migrate due to foveal development) and infants need to readjust to the new physical properties during development. Aslin and Salapatek (1975) found that infants' saccades towards peripheral stimuli often undershot the target within the first two months of life (hypometric saccades); infants initially fixated on a position closer to the centre, followed by several corrective saccades. This inaccuracy reflects another difficulty in attention shift tasks that is overcome during development.

In summary, infants' ability to shift attention improves with age, reflected by shorter saccadic latencies, less sticky fixations and more accurate saccade execution.

1.3.2 Implications of the FSP for clinical populations

An impaired ability to switch attention in the competition condition of the FSP can be found in several developmental disorders, for example in children with Williams Syndrome (Atkinson et al., 2003), pre-term born infants (Atkinson et al., 2008), siblings of autistic children (Elsabbagh et al., 2009; Gliga, Jones, Bedford, Charman, & Johnson, 2014), infants with hypoxic-ischaemic encephalopathy (HIE, Mercuri et al., 1997; Mercuri et al., 1999) and children who had one of their brain's hemispheres removed (hemispherectomised children, Braddick et al., 1992). Delayed development of the ability to disengage predicts later impairments in inhibitory attentional control at school age (Hitzert, Van Braeckel, Bos, Hunnius, & Geuze, 2014). The FSP can therefore be used as an early indicator of delayed development (review: Atkinson & Braddick, 2011; review: Atkinson & Braddick, 2012; Atkinson et al., 2008).

Due to its prognostic validity the FSP can serve as an outcome measure to investigate the effectiveness of treatments for the above mentioned conditions and the cognitive deficits going along with them. Many tests of attention function can only be used from preschool and school age on, as there are almost no cognitive tests before 1 year and the number of tests is limited for ages between 1 and 4 years, meaning that treatment outcomes cannot be investigated before this age (e.g. Lucas et al., 1998). However, delays in development can lead to further cognitive and social impairments (Hunnius, 2007), making it desirable to intervene early. The FSP can be deployed from

birth on, allowing for an early evaluation of improvements in cognitive functions. Neurodevelopmental studies suggest that an overproduction of synapses in the first two years of life allows the brain to show more plasticity, allowing for an early correction of disorders, while later intervention is less successful (e.g. Burkhalter, 1993; de Haan & Johnson, 2003b; Huttenlocher, 1979; Huttenlocher, de Courten, Garey, & Van der Loos, 1982; Petanjek et al., 2011). Development in this age is more flexible, while connections are less likely to be established later in life (de Haan & Johnson, 2003b) making it desirable to intervene in this early period to support normal age-based development. Possible interventions include behavioural changes (e.g. Assaf, 1982), or medical and dietary interventions (e.g. Blakstad et al., 2015; Koletzko, Schmidt, Bremer, Haug, & Harzer, 1989; Lucas et al., 1998). The FSP provides an outcome measure for these interventions.

Some of the neurodevelopmental disorders described above coincide with language impairments, while in other syndromes language and attention can be independent of each other (e.g. Bellugi, Marks, & Sabo, 1993). It is therefore possible that patients with language impairments have a normal ability to shift attention; however the frequently used methods are unfair to these populations. This is one of the reasons why it is crucial to develop and use nonverbal tests of brain mechanisms of attention that are fair to nonverbal populations, alongside the opportunity that these tests provide for testing pre-verbal infants.

Chapter 3 describes the development of a version of the FSP using eye-tracking, which could be used as a clinical measure both for detection and monitoring of treatment progress. Chapter 4 combines the eye tracking monitoring of saccades with EEG to allow a nonverbal investigation of neural attention mechanisms. Chapter 6 establishes a baseline of brain mechanisms in typically developing infants, which can be used as a starting point to investigate deviations from the normal development in the above mentioned risk groups.

In summary, the FSP can be used as a non-verbal measure of attention development in typically and atypically developing infants, to predict later developmental outcomes and to monitor the efficiency of interventions. It prompts speculations about neural development; however, direct studies of brain mechanisms in the FSP are rare. Therefore, the current thesis aimed to develop a direct measure of neural responses during attention shifts.

1.4 Brain mechanisms in normal adults

The brain mechanisms of attention are complex and involve various areas and circuits of the brain. Distinct brain networks for attention can be identified, which in turn influence other brain networks for visual processing (Posner & Rothbart, 2007). To investigate visual attention mechanisms it is therefore important to understand both the visual pathways, and the brain structures and networks that modulate them (Corbetta, 1998). *Figure 1.4* provides an overview to visualise the relationships between visual processing and attention that need to be considered. This section begins with an overview of research on healthy adults, describing the brain processes involved in visual processing before summarizing the brain areas involved in visual attention and reviewing models on how they interact as attention networks that modulate visual networks. It will then go in more specific detail on the attention networks involved in shifts of attention. After an overview of typical brain mechanisms in healthy adults, differences in patient groups and infants will be discussed.

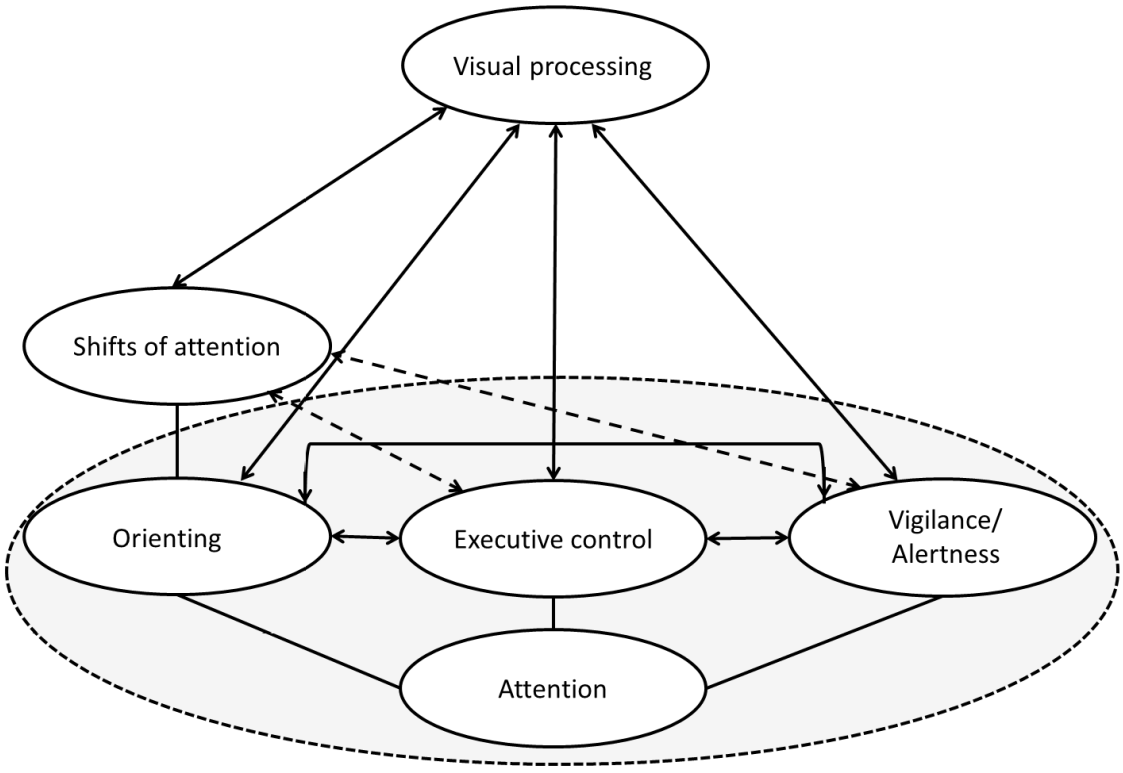


Figure 1.4. Interaction of brain mechanisms involved in visual processing and attention. To understand the brain mechanisms of visual attention, brain networks responsible for different attentional functions and for visual processing need to be considered. Different attentional functions can be separated and influence each other. The ability to shift

attention is part of the orienting function. All attentional functions can affect visual processing and are in turn affected by visual processing, suggesting that it is important to consider brain mechanisms of both visual processing and attention when investigating neural mechanisms of visual attention.

1.4.1 Visual processing

Visual information arriving at the retina is passed on through the optic nerve to the lateral geniculate nucleus (LGN) from where the optic radiation transmits it to the primary visual cortex (striate cortex), where simple target features are processed (e.g. Casagrande & Kaas, 1994; Hubel & Wiesel, 1962). The information is then passed on to higher-order visual areas (Casagrande & Kaas, 1994) along two different pathways. The occipitotemporal pathway, or ventral stream, is involved in object identification, and the occipitoparietal pathway, or dorsal stream, is involved in spatial processing (e.g. Atkinson & Braddick, 2003; Goodale & Milner, 1992; Milner & Goodale, 1995; Mishkin, Ungerleider, & Macko, 1983).

Attention can modulate neural responses along different steps of processing in both of these pathways as shown by electrophysiological recordings in non-human primates (e.g. Robinson, Goldberg, & Stanton, 1978), psychophysical and lesion studies in humans (for reviews see: Mangun, Hillyard, & Luck, 1993; Posner & Petersen, 1989; L. H. Snyder, Batista, & Andersen, 2000) and human MRI studies (e.g. Saber, Pestilli, & Curtis, 2015) and thereby influence different ways of information processing. Top-down attention leads to an increased activation of the areas corresponding to the features or locations that are being attended. For example attending to object features leads to a modulation along the ventral stream, and spatial attention induces modulations in the dorsal stream (Posner & Dehaene, 1994) as well as enhanced processing of the stimuli in that location in ventral processing areas, as suggested by brain recordings in non-human primates (Luck, Chelazzi, Hillyard, & Desimone, 1997; Moran & Desimone, 1985; J. H. Reynolds, Pasternak, & Desimone, 2000) and fMRI in humans (Kastner, De Weerd, Desimone, & Ungerleider, 1998). In general, brain responses to a stimulus are enhanced when attention is involved (e.g. Harter & Aine, 1984), allowing a deeper processing of an attended stimulus that can be achieved through an interaction of several different brain structures (Posner & Rothbart, 2007). The selection of the target, comparable to the engagement with a stimulus in the three steps of an attention shift in the FSP (Colombo, 2001; Hood & Atkinson, 1993; Posner

& Cohen, 1984), is supported by excitatory mechanisms. For example, attention affects spiking activity of single neurons, leading to an increased response of single cells towards attended stimuli in monkeys (e.g. Goldberg & Wurtz, 1972b; J. H. Reynolds et al., 2000) increased response amplitudes in human subjects (e.g. Di Russo, Spinelli, & Morrone, 2001; Eason, Harter, & White, 1969; Hopfinger, Jha, Hopf, Direlli, & Mangun, 2000; Keitel, Andersen, Quigley, & Müller, 2013; Morgan, Hansen, & Hillyard, 1996; M. M. Müller, 1998; M. M. Müller & Hillyard, 2000; Vialatte, Maurice, Dauwels, & Cichocki, 2010) and increased power in steady-state responses (e.g. Di Russo et al., 2001; Hopfinger et al., 2000; Keitel et al., 2013; Kim, Grabowecky, Paller, Muthu, & Suzuki, 2007; Morgan et al., 1996; M. M. Müller, 1998; M. M. Müller & Hillyard, 2000; Vialatte et al., 2010). Simultaneously, responses to distracting stimuli are suppressed, supported by inhibitory mechanisms in the brain (e.g. Humphreys, Allen, & Mavritsaki, 2009; Kastner & Ungerleider, 2000). Mechanisms similar to this inhibition may be crucial for the disengagement during attention shifts in the FSP. In summary, attention to object features or locations increases neural responses, while unattended stimuli elicit decreased responses. The FSP requires subjects to disengage attention from a central stimulus and engage with a peripheral target, suggesting that the response to the central stimulus should decrease while the response to the peripheral target increases.

The magnitude of visual responses and their attention modulations is not universal but depends on external factors, for example the number of stimuli that are present in the visual field (Keitel et al., 2013; Luck et al., 1997; Moran & Desimone, 1985). Single cell recordings in non-human primates (Moran & Desimone, 1985) and steady-state visually evoked potential studies in humans (Keitel et al., 2013) show that neural responses to a stimulus are greater when only one stimulus is visible than when other distractors are simultaneously presented, indicating a modulation of the visual response depending on stimulus number. In addition to the visual response, the effect of attention also depends on the number of stimuli, being larger the more stimuli are visible (Luck et al., 1997). The increase of steady-state visually evoked potential (SSVEP) amplitudes due to attention is bigger than the decrease in amplitudes due to presence of competitors (Keitel et al., 2013); therefore attention effects can still be clearly observed if several stimuli are presented.

In summary, attention can modulate processes along visual processing pathways, leading to enhanced processing of relevant information and inhibition of distractors. Effects depend on the visual context.

1.4.2 Areas involved in attention modulation

The previous section summarised areas involved in visual processing and the effects attention can have on them. The following section summarises areas involved in attention modulation and eye movements (*Figure 1.5*) and reviews research on how they are connected.

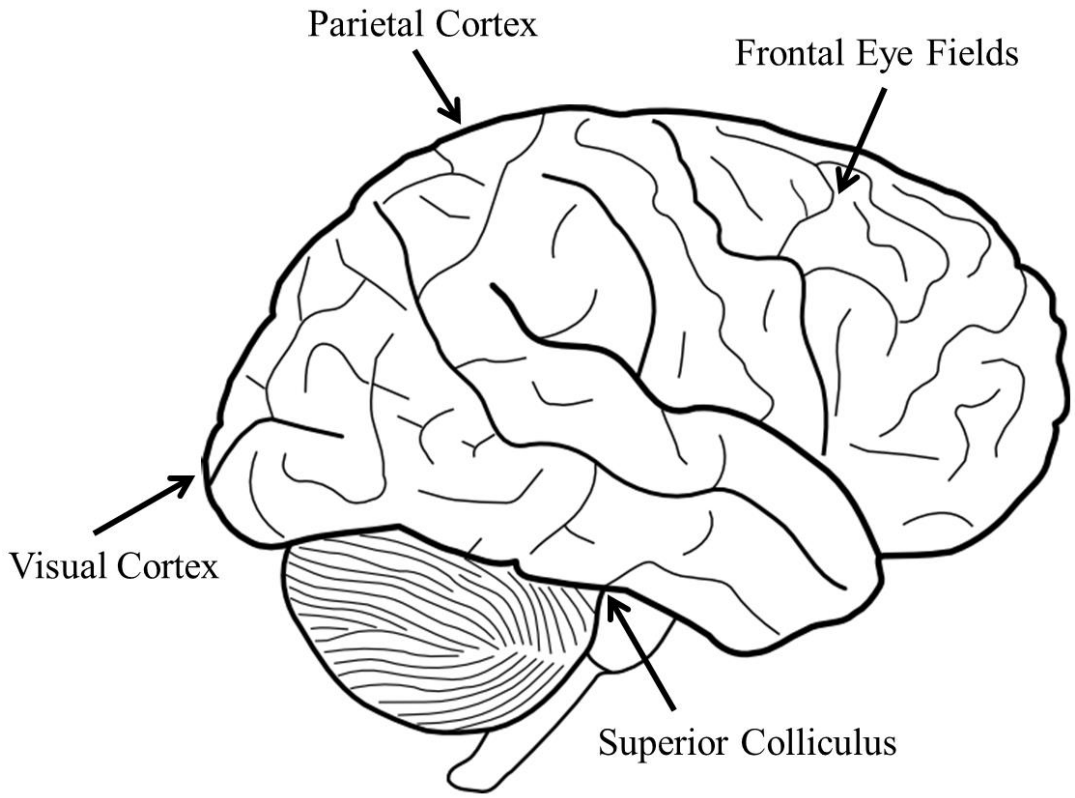


Figure 1.5. Schematic overview of brain areas involved in attention, including the superior colliculus, the visual cortex, frontal eye fields and the parietal cortex.

Superior colliculus

The superior colliculus (SC) plays a crucial role in the generation of eye-movements. SC is directly connected to premotor circuits of the brain stem that generate saccades (e.g. Hanes & Wurtz, 2001; review of primate literature: Wurtz & Albano, 1980). Recordings from SC neurons in rhesus monkeys demonstrate that lower layers showed activation 50-200 ms prior to eye-movements (Schiller & Stryker, 1972; Wurtz

& Goldberg, 1972) and stimulation of SC elicits eye-movements (Schiller & Stryker, 1972). Inactivation of SC neurons in monkeys (Sparks, 1988) and lesions can lead to impairments in saccade execution (Schiller & Tehovnik, 2005). After inactivation of SC saccades are slower (longer latencies, lower velocity) and less accurate (hypometric, Hanes & Wurtz, 2001; Mohler & Wurtz, 1977). In contrast, stronger activation of SC coincides with shorter saccade latencies, as shown by fMRI studies in human subjects (Neggers, Raemaekers, Lampmann, Postma, & Ramsey, 2005). Neggers et al. (2005) suggest that SC activation needs to reach a specific threshold for a saccade to be executed, making eye-movements more likely when SC activation in the relevant part of the spatial map is higher.

In addition to its involvement in saccade generation, neuron recordings in monkeys furthermore suggest that superficial layers of the SC respond to visual stimuli (Goldberg & Wurtz, 1972a; Schiller & Stryker, 1972). SC receives input from the early visual cortex, including V1, V2 and MT (Collins, Lyon, & Kaas, 2005; Schiller & Tehovnik, 2005).

Previously it has been suggested that SC is mainly involved in involuntary, reflexive mechanisms of directing attention, whereas cortical areas are involved in voluntary control (Crowne, 1983). fMRI studies on human subjects show that a stimulus offset in the gap paradigm activates SC suggesting its involvement in reflexive disengagement of attention (Neggers et al., 2005). Recent neuronal recordings in rats using a classical conditioning paradigm found SC neurons responding during voluntary disengagement of attention (Ngan et al., 2015); however, it is unclear whether this activation was directly related to attentional disengagement or an indirect activation as a result of disengagement caused by other areas.

In summary, SC is crucial for saccade execution and fine tuning (e.g. accuracy and speed) and potentially also involved in disengagement of attention. The EEG methodology used in this thesis preferably registers signal from cortical areas, while SC lies in deeper areas; however, its connections to visual and higher cortical processing areas play a crucial role to consider when studying overt shifts of attention.

Visual cortex

The primary visual area (V1) quickly responds to visual stimulation as early as 30 ms after target onset, as suggested by intracerebral recordings in epilepsy patients (Kirchner, Barbeau, Thorpe, Régis, & Liégeois-Chauvel, 2009) and macaque monkeys (Schmolesky et al., 1998). Human VEP recordings show that attention modulates these visual responses from around 75 – 250 ms after target onset, increasing amplitudes of an early positive visual response (Harter, Aine, & Schroeder, 1982; Heinze, Luck, Mangun, & Hillyard, 1990; Hillyard, Vogel, & Luck, 1998; Luck, Heinze, Mangun, & Hillyard, 1990; Mangun & Hillyard, 1988; Rugg, Milner, Lines, & Phalp, 1987) and the following negativity (Hillyard et al., 1998; Mangun & Hillyard, 1990). The early occipital modulations (80-130 ms) were localised over the occipital scalp region contralateral to the attended hemifield using positron emission topography (PET) (Heinze et al., 1994) and later fMRI studies confirmed modulations to occur in visual areas (e.g. Brefczynski & DeYoe, 1999; Somers, Dale, Seiffert, & Tootell, 1999). In summary, visual areas are modulated by attention.

There is furthermore a close relation between visual stimulation and saccade execution. Electrical stimulation in rhesus monkeys has shown that stimulation of upper layers of V1 and V2 inhibited saccades whereas stimulation of lower layers resulted in facilitation (Schiller & Tehovnik, 2005), indicating that visual areas might also be directly involved in overt shifts of attention, possibly due to visual input eliciting saccades.

In summary, responses in visual areas are modulated by attention and may be involved in saccade initiation.

Frontal eye-fields

The prefrontal cortex (PFC) can modulate processing in other brain regions, for example through top-down signals (review: Miller, 2000) and synchronisation with early visual areas (Kimchi, 2009). In particular, the frontal eye-field (FEF) is involved in saccade control and attention. It contains recipient neurons as well as projecting neurons, as suggested by electrode recordings and stimulation in monkeys (Sommer & Wurtz, 2004) and is widely interconnected with other areas of the brain. For example it contains connections from and to SC (review: Crowne, 1983; inactivation and

stimulation in monkeys: Hanes & Wurtz, 2001). Simulation studies in monkeys show that FEF can be activated from SC through the mediodorsal thalamus (MD) (Sommer & Wurtz, 2004). Human fMRI research suggests that FEF can inhibit saccade neurons in the SC (Neggers et al., 2005), allowing control of the saccades that are elicited by SC. It furthermore receives input from visual (Sommer & Wurtz, 2004) and other cortical areas (Crowne, 1983). Additional direct projections to thalamic nuclei for saccade execution have also been suggested (Crowne, 1983), however Hanes and Wurtz (2001) suggest that the quality of eye-movements generated by FEF stimulation in monkeys depends on the intactness of SC questioning the direct connection between FEF and brainstem oculomotor nuclei. For example lesions in SC have stronger effects on saccade execution than lesions in FEF (review: Crowne, 1983).

The functions of FEF include modulation of saccade generation, by suppressing unwanted or reflexive eye-movements (Guitton, Buchtel, & Douglas, 1985; Henik, Rafal, & Rhodes, 1994; Miller, 2000; Neggers et al., 2005; Peelen, Heslenfeld, & Theeuwes, 2004; Pierrot-Deseilligny, Rivaud, Gaymard, & Agid, 1991; Rafal, Machado, Ro, & Ingle, 2000; Shipp, 2004) and target selection (Schiller & Tehovnik, 2005). Stimulation of FEF can produce saccades towards the side contralateral to the stimulation in humans (Blanke et al., 1999) and lesions in FEF impair the ability to shift gaze to the contralateral side and can lead to neglect (e.g. Crowne, 1983). Lesion in human patients show that FEF particularly plays a role in disengagement of attention (Rivaud, Müri, Gaymard, Vermersch, & Pierrot-Deseilligny, 1994). Although many studies describe FEF activation in relation to saccades, FEF can also be involved in target discrimination without saccade execution, as transcranial magnetic stimulation (TMS) over FEF impairs perceptual sensitivity (O'shea, Muggleton, Cowey, & Walsh, 2004). Micro-stimulation studies on monkeys (Moore & Fallah, 2004) and functional magnetic resonance imaging studies in human adults (Saber et al., 2015) indicate that stimulation of FEF improves detection of luminance changes, thereby improving visual perceptual sensitivity. This effect is similar to previously found attention modulation (e.g. Di Russo et al., 2001), indicating that FEF might be involved in attentional modulation of visual processing. Intracerebral recordings in human patients suggest that FEF already shows very early responses to visual stimuli, starting around 45 ms after target onset (Kirchner et al., 2009), suggesting that FEF is activated over fast pathways. Due to FEF's interconnectedness Thompson and Bichot (2005) suggest that in the FEF area bottom-up target salience inputs and top-down goals that are learned over time are

combined to determine the most salient location to move the eyes to. *In summary the FEF is involved in saccade control and attentional modulation of visual processing.*

Parietal cortex

Similar to the FEF, areas of the parietal cortex have also been linked to attentional control, in particular the posterior parietal cortex (PPC), the lateral intraparietal area (LIP), the right temporoparietal junction and precuneus. Parietal modulation of attention-related ERPs usually occurs contralateral to the attended hemi field (review: Harter & Aine, 1984), but responses are partially right-lateralised (Posner & Dehaene, 1994). PPC is involved in attentional selection through synchronisation with early visual areas (review: Kimchi, 2009). Areas in the PPC are involved in both overt and covert attention shifts, as has been found in studies on humans with parietal lobe impairments (e.g. Pierrot-Deseilligny, Rivaud, et al., 1991; Posner et al., 1984) and in single cell recordings in monkeys (reviews: Culham & Kanwisher, 2001; Kimchi, 2009; Mountcastle, 1978; Posner & Dehaene, 1994). The lateral intraparietal area (LIP), a subdivision of the inferior parietal lobe, is hypothesised to contain a topographic visual representation of the locations of salient objects (Gottlieb, 2007). This area receives inputs from numerous areas of the extrastriate cortex, including V2, V3, V4, MT, PO and IT (review: L. H. Snyder et al., 2000). Event-related functional MRI studies show that the intraparietal sulcus is involved in voluntary orienting of attention, showing a sustained response when attention is directed to a spatial location (Corbetta et al., 2000). The right temporoparietal junction and precuneus were involved in bottom-up target detection (Corbetta et al., 2000). Precuneus seems to be involved in covert attention shifts between objects (Nagahama et al., 1999; Peelen et al., 2004). In studies of covert attention an *early directing attention negativity* can be measured in parietal areas, a negative polarity deflection that occurs 200-400 ms after cue onset contralateral to a cued location (Harter et al., 1982; Hopfinger et al., 2000; Mangun & Hillyard, 1988), indicating that these areas play an important role for attention shifts. Corbetta et al. (2000) suggest a dissociation of intraparietal areas for attentional control and temporoparietal areas for reflexive attention.

In summary, different interconnected areas have been found to be crucial for attention, including SC, visual areas, FEF and the parietal cortex. Table 1.1 summarizes brain areas involved in attention and their main functions as determined by

previous research. The following section will review models on how these areas interact.

Table 1.1. *Overview of major brain areas involved in attention and their main functions as suggested by previous literature.*

Brain area	Abbr.	Main functions
Superior Colliculus	SC	- Saccade execution - Accuracy of saccades
Visual Cortex	VC	- Visual responses increase with attention - Stimulation can initiate or inhibit saccades
Frontal Eye Fields	FEF	- Saccade control (inhibition of SC) - Attentional disengagement - Attentional modulation of perceptual sensitivity
Parietal Cortex	PC	- Attention shifts - Bottom-up target detection

1.4.3 Neural models of attention networks

Attentional modulation at different levels in the brain can begin before visual stimuli appear (Colby et al., 1996; Driver & Frackowiak, 2001) indicating that attentional preparation can take place independently of visual input. Different models have been suggested to explain how the brain areas involved in attention interact to lead to processing advantages. This section reviews brain networks of attention, starting with a separation of networks depending on the type of attentional task (e.g. Posner & Rothbart, 2007) and then focusing on the networks involved in attention shifts, which are the centre of this thesis. The networks suggested for attention shifts will be discussed in more detail, comparing top-down and bottom up attention (Corbetta & Shulman, 2002), mechanisms of disengagement and covert and overt attention shifts.

Networks for different attentional functions

Different attention networks can be separated by different behavioural attention functions. For example, Posner and his colleagues have put forward a three networks

model. Behaviourally, the first network is involved in orienting, the second in executive control and the third in vigilance or alertness (e.g. Fan, McCandliss, Sommer, Raz, & Posner, 2002; Posner & Petersen, 1989; Posner & Rothbart, 2007). Separate brain networks for these functions have been established in adults and children (e.g. with fMRI: Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; review: Posner & Rothbart, 2007). The shifts of attention that are subject of this thesis can be compared to the orienting function. Orienting of attention involves three distinct steps, which involve a network of superior parietal areas, the temporal parietal junction, frontal eye fields and the superior colliculus (review: Posner & Rothbart, 2007). An initial disengagement from the current location of attention involves the parietal lobe. It is followed by a shift of attention involving the superior colliculus and frontal eye-fields and an engagement with the new location, involving the pulvinar nuclei of the thalamus (review: Posner & Rothbart, 2007), see *Figure 1.6*. This theory is in line with other accounts distinguishing a subcortical orienting system responsible for simple engagement with a target and a cortical system responsible for more controlled directing of attention, allowing for disengagement from previous stimuli (e.g. neurodevelopmental review: Atkinson & Braddick, 2011; review of cortical (FEF) compared to subcortical attention: Crowne, 1983). However, it suggests that the cortical frontal eye-fields are involved in simple shifts as well. Diffusion tensor imaging (DTI) studies investigating the white matter tracts involved in different attention functions showed that orienting behaviour correlates with the structure of the splenium of the corpus callosum, indicating that interhemispheric connections are important for orienting attention (Niogi, Mukherjee, Ghajar, & McCandliss, 2010). Brain networks involved in functions other than orienting include a network for signal detection involving the anterior cingulate (theory: Posner & Petersen, 1989; review: Posner & Rothbart, 2007), as well as lateral ventral areas, prefrontal areas and basal ganglia (review: Posner & Rothbart, 2007) and a network for alerting using right-lateralised norepinephrine pathways including the locus coeruleus, right frontal cortex and parietal cortex (e.g. fMRI: Fan et al., 2005; review: Posner & Rothbart, 2007). As the main subject of this thesis is orienting of attention, I will concentrate on the orienting network as most likely to be involved in the shifts of attention in the FSP. However, general alerting and signal detection might be additional factors that can influence the performance of subjects independent of the main task.

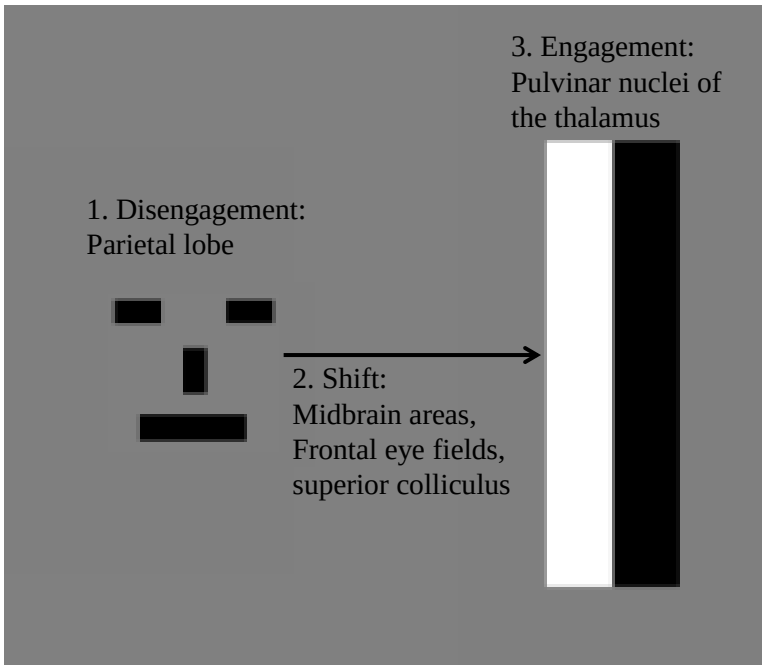


Figure 1.6. A shift of attention from the schematic face to the bars involves three different steps that are likely to involve different brain networks.

Networks for attention shifts

Both subcortical areas, such as the superior colliculus (SC) and oculomotor nuclei (e.g. investigated in physiological recordings in monkeys, review: Mountcastle, 1978; lesion studies in patients: Posner et al., 1982; lesion studies in the cat: Sprague & Meikle, 1965) and cortical areas, such as the posterior parietal cortex (PPC, e.g. review: Culham & Kanwisher, 2001; Kimchi, 2009; primate studies review: Mountcastle, 1978; human lesion studies: Pierrot-Deseilligny, Rivaud, et al., 1991; Posner et al., 1984) the prefrontal cortex (PFC, reviews: Kimchi, 2009; Miller, 2000), including the frontal eye-field (FEF, e.g. in patients after unilateral frontal lobe removal: Guitton et al., 1985; human lesion studies: Pierrot-Deseilligny, Rivaud, et al., 1991; primate brain recordings: Thompson & Bichot, 2005) are part of the networks controlling attention processing. The differentiation of cortical and subcortical structures was the focus of early accounts of attention shifts (Bronson, 1974), suggesting that subcortical areas are relevant for reflex-like directing of attention, while cortical areas are necessary for more controlled voluntary shifts of attention. Evidence has confirmed the role of subcortical structures in reflexive attention (e.g. hemispherectomy study: Braddick et al., 1992; human lesion studies: Rafal et al., 2000) and demonstrates that cortical areas can modulate them to control attention shifts (reviews: Crowne, 1983; Kimchi, 2009;

Miller, 2000). Schiller (1985) suggests a model for eye-movement control in which a channel involving the subcortical SC is responsible for reflexive saccades to salient stimuli, whereas an FEF channel controls eye movements towards complex stimuli that require a detailed analysis of visual information. Both channels are modulated by inhibition through the substantia nigra (Schiller, 1985). This model can be relevant for explaining the brain mechanisms of reflexive saccades occurring in the non-competition condition of the FSP and the more controlled saccades under competition. However, brain mechanisms of attention have been suggested to involve more complex processes than explained by a cortical and subcortical dichotomy (see e.g. neurodevelopmental approaches: Atkinson, 1984; M. H. Johnson, 1990) and will be discussed in the following section.

Top down and bottom up networks

Corbetta and Shulman (2002) differentiate separate forms of orienting and distinguish cognitive (top-down/endogenous) and stimulus-driven (bottom-up/exogenous) orienting of attention. They suggest that both types involve two distinct but interacting attention networks. Top-down attention is hypothesised to involve a network of visual areas, intraparietal sulci and frontal eye-fields (dorsal network), whereas bottom-up attention involves a right-lateralised network including the temporoparietal junction and the ventral frontal cortex (ventral network, see *Figure 1.7*) (Corbetta & Shulman, 2002, 2011). Functional connectivity magnetic resonance imaging (fMRI) studies on neglect patients support the view that connections within dorsal and ventral attention networks play a crucial role in spatial attention (He et al., 2007). The ventral network is related to orienting, vigilance and saliency detection, whereas the dorsal network is thought to control spatial attention (summarised by He et al., 2007). Behavioural research supports the idea that the brain network involved in shifts of attention is right-lateralised, as warning stimuli to the right hemisphere had a greater facilitation effect on responses than towards the left hemisphere (Heilman & Van den Abell, 1979).

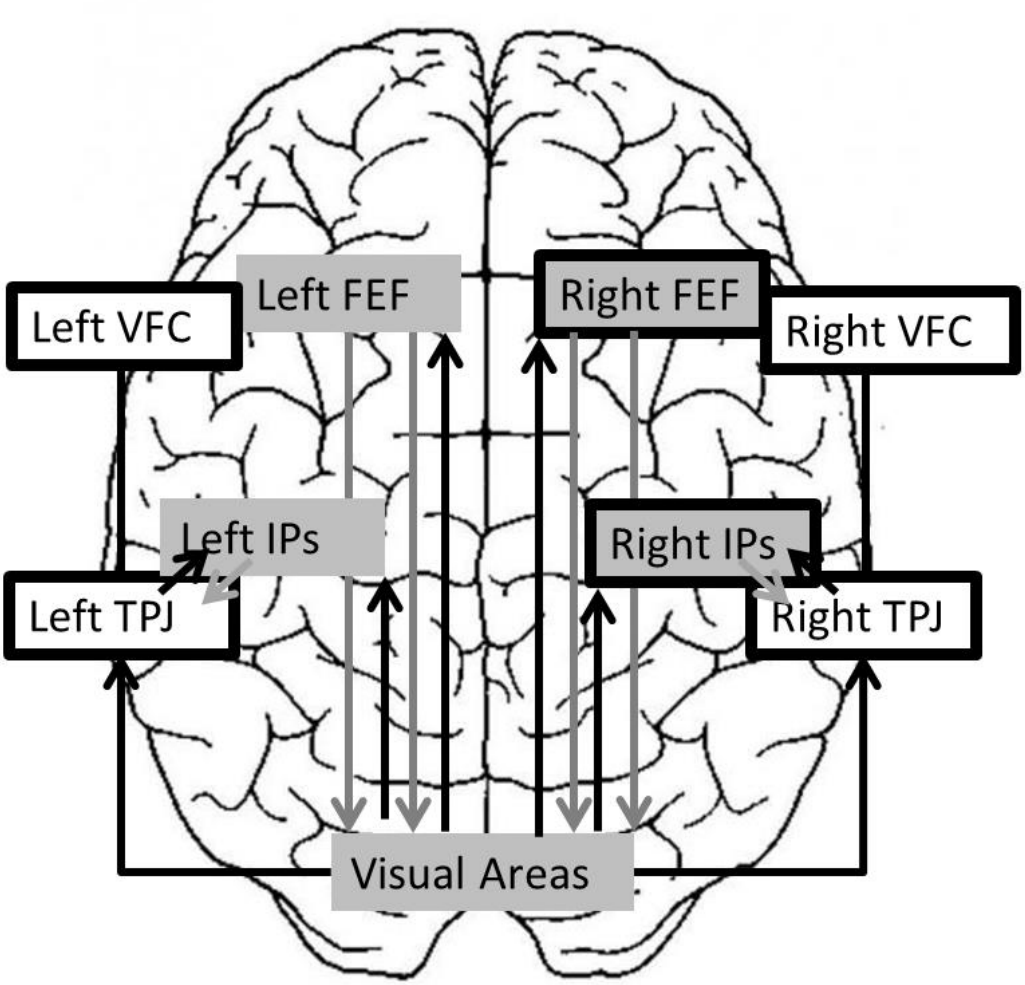


Figure 1.7. Differentiation between the dorsal (grey background) and the ventral (black outline) fronto-parietal network as suggested by Corbetta and Shulman (2002). The dorsal network involves connections from frontal eye-fields (FEF) and intraparietal sulcus (IP) to visual areas. The ventral network involved the temporoparietal junction (TPJ) and the ventral frontal cortex (VFC) and only overlaps with the right dorsal network (black outline and grey background).

Some research using fMRI suggests that the neural mechanisms of endogenous and exogenous attention involve similar networks including premotor cortex, posterior parietal cortex and frontal cortex (Peelen et al., 2004). Although similar areas were found to be involved in attention shifts as suggested by Corbetta and Shulman (2002), Peelen et al. (2004) found no difference in activation between the two networks and suggest that previously found differences might be confounded with task differences, for example due to general arousal or eye-movements.

In general brain areas involved in top-down and bottom-up attention overlap and it is debated whether different networks are involved in both mechanisms. In the FSP used in this thesis attention is mainly directed bottom-up, as the attention shift is related to the appearance of a salient stimulus, the location of which is randomised and therefore cannot be predicted by top down mechanisms. According to Corbetta and Shulman (2002) a right-lateralised network would be more prominently involved in this bottom-up shift, whereas Peelen et al. (2004) suggests more widespread involvement of different networks.

Brain mechanisms of disengagement

Only very few studies have directly looked at the brain mechanisms involved in disengagement of attention during overt shifts, for example using EEG to measure brain potentials before saccadic shifts in adults and 6 months old infants (Csibra, Johnson, & Tucker, 1997; Csibra, Tucker, & Johnson, 1998) and pre-saccadic ERPs in adults with autism (Kawakubo et al., 2007). Csibra et al. (1997) examined saccade-locked potentials and describe a slowly developing positivity in centro-parietal areas that they suggest to be related to saccade planning. Kawakubo et al. (2007) showed higher peak amplitudes of this pre-saccadic positivity in adults with autism than in controls when they were doing an overlap task and interpret that a longer and higher activation is necessary to reach a threshold for saccade execution in individuals with autism. Brain recordings in rats furthermore suggest an involvement of the superior colliculus in disengagement (Ngan et al., 2015). In summary, frontal and parietal areas have mainly been found to be involved in disengagement in human subjects.

Brain mechanisms of covert vs overt shifts

Covert attention commonly involves attention over a sustained period of time of some length. For example, in simple cuing paradigms subjects attend to a location or object for the time until the target appears. In contrast, overt attention shifts usually involve a direct response to a target without preceding attention to its location and usually coincides with an eye movement towards the target. An MRI study by Corbetta et al. (1998) suggests that similar brain areas are involved in covert attention shifts, as in overt shifts. An fMRI study of covert and overt attention shifts confirmed that the brain mechanisms of both shifts mainly overlap; however, overt shifts show more activation in parietal and frontal regions (Nobre, Gitelman, Dias, & Mesulam, 2000). Saber et al.

(2015) suggest that saccade planning can enhance brain activity related to visual processing, leading to an advantage in attention during overt shifts. The majority of EEG studies investigated covert shifts of attention, as overt eye-movements can cause artefacts in ERP data. Experiments described in Chapter 4 compare covert and overt attention shifts towards the same stimuli in adults involving a response to a target in both overt and covert conditions to establish a baseline for comparison of previous covert attention shift studies with this thesis.

In summary, different neural attention networks can be distinguished by function (orienting, executive control, vigilance/ alertness) and within the orienting network specific models of different types of attention shifts can be differentiated. Networks are based on a variety of studies using MRI, in-brain recordings, stimulation and other techniques. However, due to methodological difficulties, non-invasive recordings of neural activity during overt attention shifts are rare. The current thesis aimed at filling this gap by simultaneously recording brain responses and fixation shifts to investigate neural models of attention.

1.5 Neural abnormalities in patient groups

The previous section reviewed brain mechanisms of visual attention in healthy adults; however, attention impairments can occur in numerous patient groups and will be discussed in this section. Attention impairments can develop early in life and already be present during childhood, as in attention deficit hyperactivity disorder (ADHD, e.g. Perchet, Revol, Fourneret, Mauguière, & Garcia-Larrea, 2001), or they can be caused by congenital or acquired neural malfunctions, for example in mid-brain degeneration patients (e.g. Posner et al., 1982), or patients with parietal lobe damage (e.g. Posner et al., 1984) or in neglect patients (e.g. He et al., 2007). Abnormal behavioural patterns in patients are often similar to typical behaviours found in infants. For example patients with FEF lesions (Rivaud et al., 1994) or SC lesions (Pierrot-Deseilligny, Rosa, Masmoudi, Rivaud, & Gaymard, 1991) show impairments in attention shifts that are more pronounced under competition than non-competition conditions, comparable to the impairments found in young infants (e.g. Hood & Atkinson, 1993). Furthermore, patients with Balint's Syndrome who have bilateral parietal damage show 'sticky fixations' similar to infants (Hood, 1995). Moreover, hypometric saccades can be observed in both infants (Aslin & Salapatek, 1975) and patients with FEF lesions (Paus,

1996; Rivaud et al., 1994). *Figure 1.8* provides an overview of overlapping impairments in patients and infants.

Studying the brain lesions that cause attention impairments can further the understanding of brain mechanisms involved in the developing attention mechanisms in infants and vice versa. If behavioural deficits occur due to lesions in a specific area this suggests that this area is to some extent involved in the impaired behaviour. One view on similar deficits in infants suggests that this module has not yet fully developed. Whether this approach can tell us about the immaturity of the specific module has been vigorously debated, as the same task may involve different neural areas in infants compared to adults (e.g. Karmiloff-Smith, 2013). However, considering the details of deficits in patients can prompt speculations about underdeveloped modules in infants.

Patients with spatial neglect show deficiencies in the ability to attend to one visual hemi field, due to a lesion in the contralateral brain hemisphere (Corbetta & Shulman, 2011; Posner & Cohen, 1984). Bottom-up and top-down mechanisms of attention are equally impaired (Bays, Singh-Curry, Gorgoraptis, Driver, & Husain, 2010). Lesion studies identified lesions to the FEF (Crowne, 1983) or PPC (Posner et al., 1984) as main causes of neglect, but other areas, including interior insula, middle frontal gyrus and subcortical nuclei can lead to deficits as well (see Corbetta & Shulman, 2011 for a review). This indicates that these regions play a crucial role for shifting attention to one hemi field. Lesions in the right hemisphere of the brain more commonly cause long lasting symptoms of neglect than in the left hemisphere (Maeshima et al., 1995; Stone, Halligan, & Greenwood, 1993). This is in line with He et al. (2007) suggesting that impairments of the right-lateralised ventral attention network described by Corbetta and Shulman (2002) are mainly found in neglect patients. They furthermore found that interhemispheric connectivity in the posterior parietal cortex showed short-term impairments, with neglect being more severe the less intact the connections were. White matter damage leads to impairments (Bartolomeo, De Schotten, & Doricchi, 2007; De Schotten et al., 2005), indicating that connections between areas play an important role in the ability to shift attention. Connections are still developing in infants; hence the maturation of brain connections might play a crucial part in the development of attention, similar to the effect of lesions in patients. In summary, the deficits in neglect patients involve lesions in FEF; PPC, interior insula,

middle frontal gyrus and subcortical nuclei, all of which have been suggested to be involved in attention networks, as well as connections between both hemispheres.

Individuals with autism have difficulties disengaging their attention from a competing target, which become visible early in infancy starting between around 7 months (Elison et al., 2013) to 14 months of age (Elsabbagh et al., 2013) and persist to adulthood (Kawakubo et al., 2007). A neuronal difference between typically developing infants and infants who are later diagnosed with autism is the organisation of their corpus callosum (Elison et al., 2013), indicating that, as in neglect patients, interhemispheric connection plays a role for attention shifts in autism.

In summary, different patient groups can show impairments in the ability to shifts attention, which are sometimes similar to impairment observed in infants.

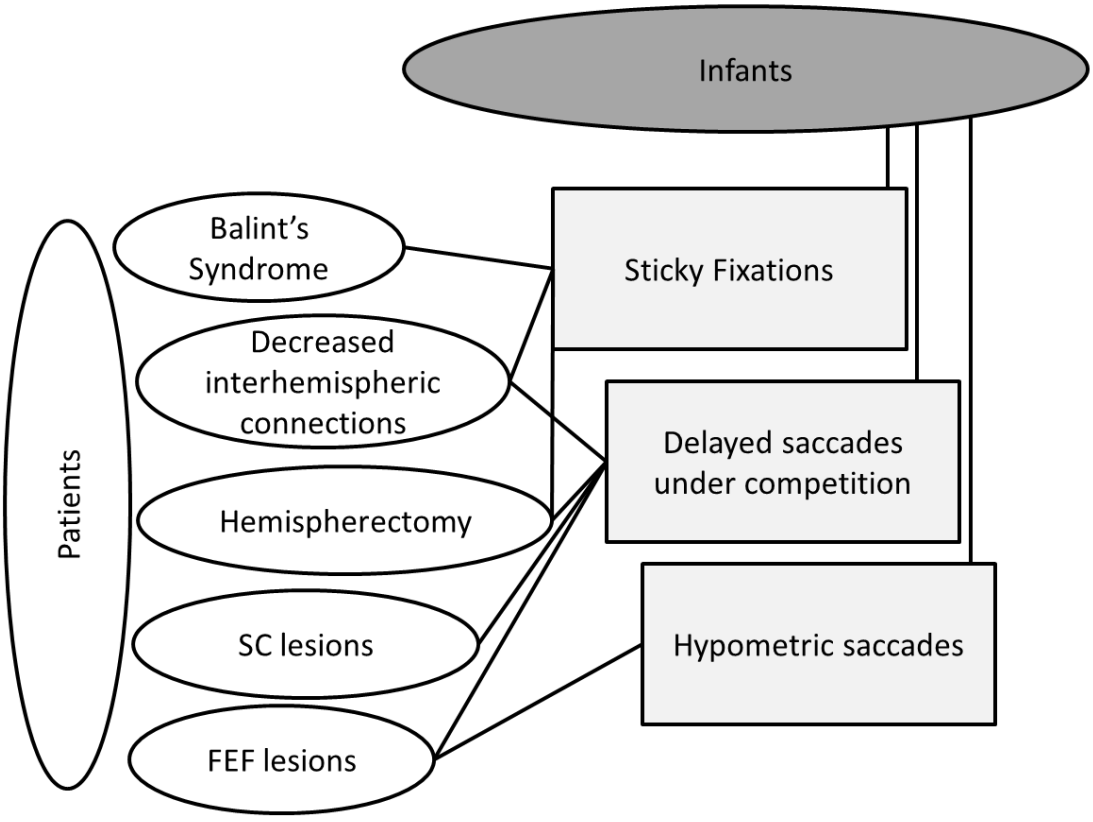


Figure 1.8. Impairments during attention shifts (square boxes) overlap between different patient groups (left) and infants (top).

1.6 Brain mechanisms in infancy

The brain changes with age with critical development taking place during infancy and childhood. This section will review both structural and functional changes, discuss how they coincide and relate developing brain networks to the infant's improving ability to shift attention.

Different accounts explain the mechanisms of neural development differently (e.g. Atkinson, 1984; review: Atkinson, 2000a; review: M. H. Johnson, 2001), see Table 1.2 for a summary. The "*maturational account*" states that specific brain areas are responsible for specific behaviours and develop with age (e.g. Atkinson, 1984, 2000a). In this view, some areas may be inactive or underdeveloped in infants and simply become active with age. The "*skill learning hypothesis*" adds a learning factor to developmental changes. It states that the brain changes when new skills are acquired and that these changes are similar during infancy as for adults. A recent, more complex approach is the "*interactive specialisation approach*". "*Interactive specialisation*" describes the idea that brain development results from both intrinsic and extrinsic factors to the infant (de Haan, Humphreys, & Johnson, 2002; M. H. Johnson, 2000). It suggests that improving behaviour can not only result from increasing activity in specific brain areas, but also from greater efficiency of neural pathways due to improved connections *between* brain areas. Furthermore, it assumes an interaction of learning with brain development (M. H. Johnson, 2000), meaning that learning can affect neural development and its effect can be different in infants and adults.

Table 1.2. *Summary of different approaches explaining neural development.*

Developmental account	**Idea**
Maturational account	Specific brain areas, responsible for a specific behaviour, develop (become functional) with age.
Skill learning hypothesis	Learning changes the brain and its effect is similar in infants and adults.
Interactive specialisation	Brain development occurs through an interaction of development of brain areas, their connectivity, their efficiency and learning.

In summary, different approaches can be used to explain neural development and they suggest that it is important to consider general brain development, the development of neural connections and the effect of learning on them. Structural and functional changes and models explaining their development will be reviewed in the following sections.

1.6.1 Structural brain development

Brain development involves, amongst others, changes in grey matter, the number of synapses and the myelinisation of connecting fibres. Numerous post-mortem studies of brain development show that synapses follow a pattern of initial exuberant growth in which numerous new connections are built, followed by a period of pruning, during which synaptic density decreases (e.g. Burkhalter, 1993; de Haan & Johnson, 2003b; Huttenlocher, 1979, 1990; Huttenlocher et al., 1982; Petanjek et al., 2011). Different cortical areas follow this developmental pattern, but the pace differs depending on the cortical area and the cortical layer. The occipital area of the cortex is developing very early in life. Its adult volume size is reached within the first 4 months (Huttenlocher, 2002), while synaptic density keeps increasing until between 4 and 8 months followed by synaptic pruning until adult synapse counts are achieved at 11 years (Huttenlocher, 2002; Huttenlocher et al., 1982). Higher-level areas like the frontal cortex develop later, peaking in synaptic density around 1 year and decreasing until 16 years of age (Coch & Gullick, 2011; de Haan & Johnson, 2003b; Huttenlocher, 1979, 2002). More recent MRI studies support the developmental pattern found in post-mortem studies on synaptogenesis (review: Toga, Thompson, & Sowell, 2014). Development furthermore differs depending on the cortical layer. The deeper cortical layers complete synaptogenesis earlier than the outer layers in V1 (Huttenlocher, 2002). Only deep layers of the cortex are substantially connected in newborns, while outer layers are less developed at birth (Huttenlocher, 2002). As intra-cortical connections mainly depart from upper cortical areas, cortical pathways are less developed in newborns (M. H. Johnson, 2002). Furthermore, myelination is completed earlier in subcortical areas than in cortical areas of the brain (Yakovlev & LeCours, 1967 in Bronson, 1974). This is in line with the account that attention involves reflexive subcortical mechanisms at birth, while more controlled cortical systems develop later (Bronson, 1974). However, subcortical and cortical growth overlap, for example morphological changes occurring in the LGN during the first months of life (De

Courten & Garey, 1982) coincide with synaptogenesis in the frontal cortex (Huttenlocher et al., 1982).

1.6.2 Functional brain development

Synaptogenesis can coincide with changes in the ERP activity measured on the scalp (Atkinson, 2000a, 2000b; Courchesne, 1990; Shibasaki & Miyazaki, 1992) and synaptic structure is linked to cortical functioning (Huttenlocher, 2002). EEG studies suggest that slow wave responses to visual stimuli stem from subcortical structures while high-frequency responses originate in cortical areas (Whittaker & Siegfried, 1983). Slow wave responses can be observed at birth, whereas high-frequency responses appear around 4 weeks of age, indicating that cortical processing evolves at that age (Schanel-Klitsch & Siegfried, 1987). Different tests have been used to link behavioural development to neural development. For example, if infants successfully complete orientation detecting, disparity detection, motion detection or fixation shift tasks, this demonstrated that various channels in the cortex have become functional (Atkinson, 1984, 2000b).

Positron Emission Tomography (PET) was used to measure functional activation of different brain areas and showed that subcortical structures and primary motor areas are active in infants younger than 5 weeks, while parietal, temporal and occipital cortical activation increases around 3 months and the last regions to become active are frontal and dorsolateral occipital regions between 6 and 8 months (Chugani, Phelps, & Mazziotta, 1987), reflecting a similar pattern to the development of synapses (Huttenlocher, 1979; Huttenlocher et al., 1982). Due to the slow increase in frontal activation, they suggest that not only the frontal cortex but other cortical areas as well are responsible for the control of reflex-like movements (Chugani et al., 1987). M. H. Johnson (2001) suggests that the adult brain's functions are more specialised than the infant brain with specific areas being responsible for different behavioural functions. Hence, although several areas might be involved in attention in infants, as suggested by Chugani et al. (1987), the cortex might become more specialised in adults. In summary, studies on synaptogenesis, EEG and PET support the idea that subcortical areas are the first to start functioning, followed by cortical sensorimotor areas and finally frontal cortical areas.

Adult research showed that functional connections between hemispheres (Niogi et al., 2010) and between cortical and subcortical structures (see Posner & Rothbart, 2007) play a crucial role for the flexible control of attention. In addition, neuroimaging studies using MRI suggest that interhemispheric connections play a crucial role in the development of attention shifts (Bartolomeo et al., 2007; De Schotten et al., 2005; Elison et al., 2013). Therefore the development of these connections might be involved attention development in infants and needs to be considered for models of attention in infancy.

In summary, structural and functional development is completed in subcortical areas before cortical areas (Chugani et al., 1987; Huttenlocher, 1979, 2002; Huttenlocher et al., 1982; Schanel-Klitsch & Siegfried, 1987), subcortical connections develop earlier than intra-cortical connections (Huttenlocher, 2002) and it is suggested that brain areas become more specialised with age (e.g. Atkinson, 2000a; M. H. Johnson, 2001).

1.6.3 Brain models of attention in infants

Different theories have been suggested to model the development of brain mechanisms of visual attention.

Subcortical and cortical dichotomy

In his early theory, Bronson (1974) proposed a "two visual systems model", postulating that vision is controlled in two different brain systems. The primary visual system involves the lateral geniculate nucleus, striate and prestriate areas in the occipital lobes and temporal lobes, whereas the secondary visual system involves only subcortical structures, including superior colliculus and pulvinar, which directly project to prestriate areas and infero-temporal cortex. These two systems are modulated by an additional pathway for eye-movement control, including feedback connections from temporal lobes to frontal eye-fields to superior colliculus and ocular motor nuclei. The secondary visual system develops earliest and processes information about the location of salient stimuli, whereas the later developing primary visual system codes more complex information regarding stimuli. According to this model, simple eye-movements towards salient targets and smooth pursuit of targets might be mediated by the subcortical secondary system and are possible without cortical involvement. This is

in line with findings from Braddick et al. (1992) that show that infants lacking one cerebral hemisphere are still able to make saccades towards salient targets, without cortical involvement. More sophisticated reactions, as a redirection of attention from one stimulus to another use the primary system involving cortical systems, including the temporal lobes (Bronson, 1974). Atkinson (1984, 2000a) developed Bronson's idea to include developing modulations of subcortical by cortical processes. The idea of early subcortical reflexive attention, and later cortically controlled disengagement has been taken up by other studies (cf. Atkinson, 2000b; Atkinson & Braddick, 2003; Hood & Atkinson, 1993; Hood et al., 1998) and the developmental improvement in the FSP under competition is taken as indirect evidence that in the first weeks of life, attention is reflex-like, involving only subcortical pathways, with cortical control emerging at about 3 months, allowing the infant to shift attention more controlled (cf. Atkinson, 2000b; Atkinson & Braddick, 2003, 2011; Hood et al., 1998). Bronson (1974) notes, however, that lesions in cortical areas in adults can interfere with subcortical reactions and impair the ability to shift attention, indicating that is it ambiguous whether attention shifts are purely subcortical or involve cortical control. If the cerebral cortex plays a crucial role for attention shifts (Braddick et al., 1992), its involvement should be measurable with EEG, which records cortical activity from the scalp surface and was therefore used to investigate cortical involvement in attention shifts in Chapter 6.

Four attention pathways

Bronson's model was used as a starting point for future explanations of attention development. However, it has been criticised for being too simplistic (Atkinson, 1984; de Haan & Johnson, 2005; M. H. Johnson, 1990; Richards, 2003b) and later research shows that several distinct cortical pathways are involved in visual processing (e.g. Goodale & Milner, 1992; Milner & Goodale, 1995; Mishkin et al., 1983) and attention (Corbetta & Shulman, 2002; Fan et al., 2005; Posner & Rothbart, 2007). More detailed models were postulated by Atkinson (1984, 2000a) and M. H. Johnson (1990), who suggests that visual processing is more complex than described by the subcortical and cortical dichotomy, involving several pathways that connect both cortical and subcortical structures. They stress the development of primary visual area (V1) is crucial for visual attention as it is interconnected with different pathways controlling saccades and attention. M. H. Johnson (1990) distinguishes several different pathways for visual processing from a developmental perspective based on an adult model

proposed by Schiller (1985). 1. An "*SC pathway*" from retina to SC is responsible for reflex-like responses, 2. An "*inhibitory pathway*", in which cortical inputs to substantia nigra (SN) lead to inhibition of the SC, regulates its reflexive activity, 3. The "*MT pathway*" from V1 to MT to SC and an additional direct pathway from V1 to SC can activate collicular activation and 4. An "*FEF pathway*" allows additional attentional control and complex visual strategies (M. H. Johnson, 1990). *Figure 1.9* visualises the different pathways.

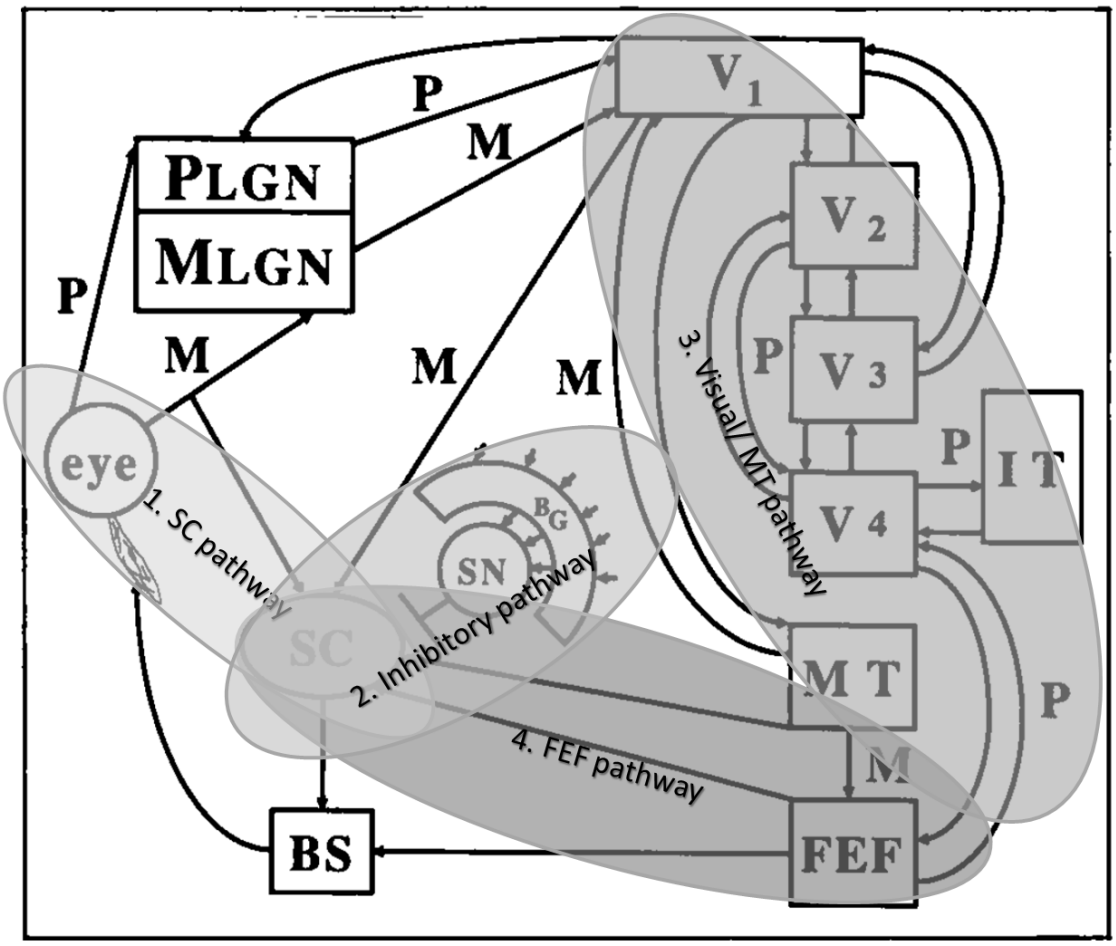


Figure 1.9. Neurodevelopmental model based on Schiller (1985), extracted from M. H. Johnson (1990) with minor alterations. Four attention pathways include the SC pathway (1) from retina to SC, the inhibitory pathway (2) from SN to SC, the Visual/ MT pathway (3) from visual areas to SC and the FEF pathway (4).

Table 1.3 summarises the developmental course of the four different pathways, visualised in *Figure 1.10*. The SC pathway has been suggested to be present from birth on allowing reflexive orienting to stimuli (Atkinson, 1984; Bronson, 1974; M. H. Johnson, 1990). Around 1 months of age the inhibitory pathway begins to modulate SC

activation through the substantia nigra. As its neuronal inhibition decreases with time, peripheral stimuli elicit saccades when the signal from the stimulus exceeds the inhibition. The cortical MT pathway is developing between 1 and 2 month of age. Between 3 and 6 months the FEF pathway is the last to develop, leading to more fine-grained regulation of the inhibition of collicular saccades (M. H. Johnson, 2002). All pathways are developed after 6 months (M. H. Johnson, 1990). Atkinson (1984, 2000b) and M. H. Johnson (1990, 2002) suggest that the ability to disengage depends on an interaction of the different pathways. Visual stimulation activates the MT and inhibitory feedback pathways (M. H. Johnson, 1990). The inhibitory feedback pathway inhibits the SC to inhibit saccades and initiate a fixation, but this inhibition decreases with time. A peripheral stimulus elicits saccades when the signal from the stimulus exceeds the inhibition. Activation through posterior visual areas (e.g. the MT pathway and the direct V1 pathway) can facilitate this leading to the threshold being reached earlier. This model can be used to explain the improvement in infants' ability to shift attention as the inhibitory pathway and top-down connections from posterior visual areas need to develop to allow disengagement.

Table 1.3. *Four different attention pathways develop at different ages and involve connections between different areas.*

Pathway	**Areas**	**Age of development**
SC pathway	From retina to SC	Birth
Inhibitory pathway	From cortex to SN to SC	1 month
MT/ visual pathway	From V1 to MT to SC and directly from V1 to SC	1-2 months
FEF pathway	From FEF	3-6 months

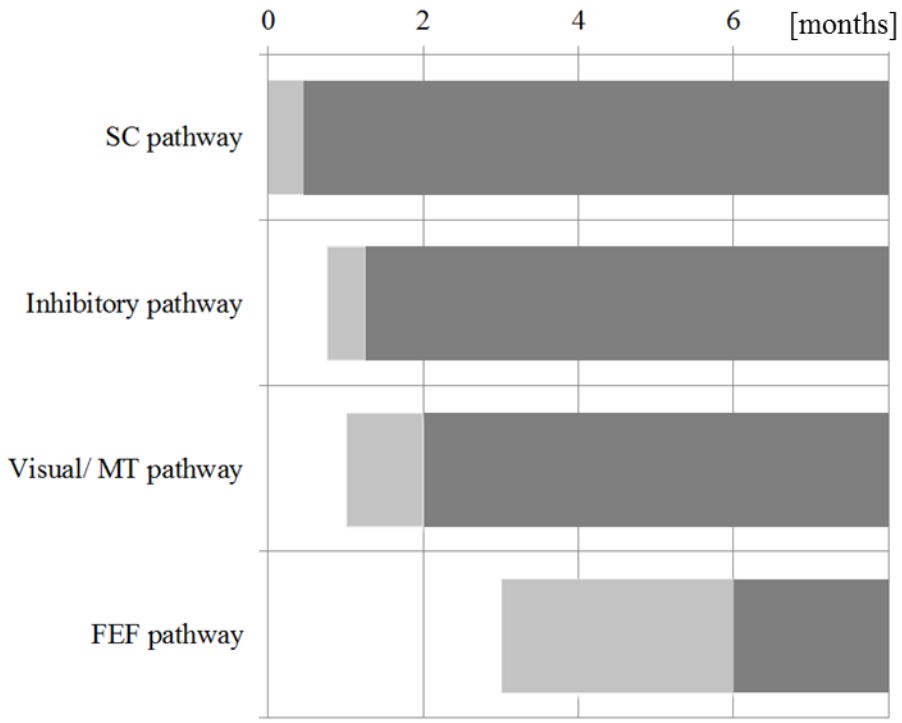


Figure 1.10. Time course of development (light grey) and activity (dark grey) of the four different attention pathways.The SC pathway is the first to become active around birth, followed by the inhibitory pathway around 1 month, the visual/ MT pathway between 1 and 2 months and the FEF pathway between 3 and 6 months.

Comparison to adults: Three distinct attention networks

The three different attention networks distinguished in adults as described above (Fan et al., 2005; Posner & Petersen, 1989; Posner & Rothbart, 2007) have also been considered from a developmental perspective (Atkinson & Braddick, 2012), suggesting that the orienting system develops from subcortical reflexive orienting to cortically controlled orienting. As reviewed above, the parietal cortex plays an important role in the disengagement when orienting attention (e.g. Posner & Petersen, 1989). Atkinson and Braddick (2003) suggest parieto-frontal systems to be involved in the development of disengagement of attention in infants as well. The parietal lobe function is developing substantially around 3 months of age (Chugani et al., 1987). Severe brain lesions during infancy can lead to impairments in the ability to shift attention in premature infants (Atkinson et al., 2008) and term born infants with hypoxic-ischaemic encephalopathy (HIE, Mercuri et al., 1997; Mercuri et al., 1999). The vigilance or alertness network is comparable to an early developing general arousal system involving connections between mesencephalic regions and the cortex, which can

generally increase attention by increasing arousal (Richards, 2001a, 2003b). Sustained attention shows in an enhanced amplitude of a negative central ERP response to attended stimuli compared to unattended stimuli (de Haan, 2007b; Richards, 2003b; Richards, Reynolds, & Courage, 2010). Richards et al. (2010) suggest that the brain areas involved in this component become more organised and therefore more efficient within the first 8 months of life. Executive functions develop later during childhood, probably involving further maturation of the prefrontal cortex (review: Atkinson & Braddick, 2012; Davidson, Amso, Anderson, & Diamond, 2006; Diamond, 2002).

In summary, infants' subcortical areas develop before cortical areas (both structurally and functionally) and therefore early reflexive visual attention is mainly controlled by subcortical structures around birth whereas interplay of connections between subcortical and cortical structures develops with age, coinciding with more controlled shifts of attention. Behavioural and structural research has prompted speculations about neurodevelopmental models, but direct measures of brain responses during attention shifts are rare. The current thesis aimed at directly investigating brain responses during attention shifts in infants to provide an experimental basis for predictions of neurodevelopmental attention models.

1.7 Summary

This chapter reviewed the literature background on attention and its brain mechanisms in adults and infants. Attention facilitates behavioural responses to stimuli. Different tasks can be used to measure behavioural advantages of attention, several of which include covert and overt shifts towards stimuli. In infants, the Fixation Shift Paradigm can be used to non-verbally measure the ability to shift attention. It shows that the ability to disengage from competing stimuli before disengaging attention develops in the first months of life and plays a crucial role for normal development, as it is impaired in different developmental disorders.

Brain mechanisms of attention involve a modulation of responses in areas generally involved in visual processing by other areas. For attention shifts, the superior colliculus, visual cortex, frontal eye-fields and the parietal cortex play a crucial role. Different models have been proposed to explain how these areas interact to form attention networks. Networks for orienting, executive control and vigilance have been widely discriminated. For fixation shifts the orienting network is most crucial. Attention

shifts in competition and non-competition condition were first hypothesised to involve cortical and subcortical networks, with SC eliciting reflexive saccades and FEF controlling them. Later work differentiated more different areas, suggesting a top-down network consisting of visual areas, intraparietal sulci and FEF and a right-lateralised bottom-up network including the temporoparietal junction and the ventral frontal cortex. Covert shifts show enhanced responses compared to overt shifts of attention. Patients with frontal or parietal lesions often show attention impairments (neglect), while in patients with autism, impairments of interhemispheric connectivity has been related to attention impairments.

The brain develops during infancy, with both structural and functional development being completed in subcortical areas first, followed by visual cortex and finally frontal areas of the cortex. Various models have been suggested to explain the changes in brain mechanisms of attention during infancy. Early accounts suggest that attention is subcortical in young infants with cortical control emerging during the first year of life. More differentiated accounts suggest four pathways, an SC, MT, FEF and inhibitory pathway that develop at different paces.

The literature review showed two main gaps in the current literature. Firstly, studies directly measuring brain mechanisms of overt attention shifts are scarce due to methodological difficulties. The first aim of this thesis was therefore to develop and test a method for investigating neural mechanisms of overt attention by combining eye tracking and EEG. Secondly, behavioural and clinical studies have prompted speculations about neurodevelopmental models of attention without direct functional evidence from neuroscientific studies. The second aim of this thesis was therefore to investigate brain mechanisms of overt attention shifts using the newly developed method and to monitor their development with age to provide functional evidence for neurodevelopmental models.

In summary, this thesis aims to shed further light on the brain mechanisms of attention in adults and infants by using a new methodology, combined eye-tracking and EEG. This method will be discussed in the next chapter.

Chapter 2 Methodology

The previous chapter outlined that many behavioural studies of attention shifts have concentrated on overt shifts, but EEG studies have mainly concerned covert shifts of attention. This thesis combined EEG and eye-tracking to investigate the brain mechanisms underlying overt shifts of attention. The current chapter will review the advantages and difficulties of this methodology and specify the methods consistently used throughout this thesis.

2.1 Evaluation of the methods

2.1.1 Measuring attention with eye-tracking

Eye-tracking is a method that is suitable for both adult and infant populations (review: Gredebäck, Johnson, & von Hofsten, 2009). Early infant attention studies have usually relied on experienced 'blind' adult observer judging the time and direction of the infant's eye movements and making a manual response (e.g Atkinson et al., 1992; Richards, 2005). This approach is subject to certain limitations, as observers cannot accurately judge saccade amplitudes and the observer's variable reaction times are added to the infant's saccade latency. Furthermore, experimenters need practice to increase the reliability of their saccade detection, making it less suitable for inexperienced personnel. To alleviate some of these limitations, other studies have used frame-by-frame video analysis, quantifying time by counting the number of frames on the tape until the eye-movement was initiated (e.g. Butcher et al., 2000; Elsabbagh et al., 2013; Hood & Atkinson, 1993; Hunnius & Geuze, 2004; Hunnius, Geuze, Zweens, & Bos, 2008; Matsuzawa & Shimojo, 1997). This approach leads to a better temporal accuracy of the saccade latencies, as the temporal resolution corresponds to the sampling rate of the camera (e.g. 40 Hz, Hood & Atkinson, 1993). However, it involves a post hoc analysis of video frames which is both time consuming and susceptible to human error (Wass, Smith, & Johnson, 2012) and results in limited spatial resolution (e.g. Morgante, Zolfaghari, & Johnson, 2012; Wass et al., 2012). Furthermore the data cannot be accessed while the experiment is running, making it impossible to regulate trial onsets on-line by using information from the gathered data.

To overcome the limitations of previous methods, nowadays eye-trackers can be used as a tool to track eye-movements with reasonably good spatial and temporal

accuracy (e.g. Gredebäck et al., 2009; Wass et al., 2012) and in investigations of fixation patterns related to underlying cognition in typically and atypically developing infants (e.g Falck-Ytter, von Hofsten, Gillberg, & Fernell, 2013; von Hofsten, Uhlig, Adell, & Kochukhova, 2009; Watanabe, Forssman, Green, Bohlin, & von Hofsten, 2012). Corneal reflection eye-trackers automatically estimate gaze positions from the reflection of a light source on the cornea relative to the pupil, with a temporal resolution depending on the video frame rate, commonly 60 Hz or greater (Gredebäck et al., 2009). They can be used to distinguish between fixations (periods of stable gaze positions), saccades (periods with high velocity of gaze) and smooth pursuits (periods during which moving objects are tracked). The eye-tracking data can furthermore be processed in real-time to automatically operate the process of the program, for example to initiate trials when the infant is fixating on the screen. This allows a shorter interval between trials, hence a larger number of trials before the infant gets tired or bored. Furthermore, once programmed, the eye-trackers can potentially be used in a clinical context without extensive operator training, as the approach can be fully automated. Appendix A summarizes a study evaluating the accuracy of data collected with eye-tracking in adult subjects to establish a baseline of data quality. It shows that the spatial accuracy of the Tobii X120 eye-tracker is sufficient for the purpose of measuring fixation shifts with many common stimuli used in infant research. In conclusion, eye-tracking is a useful tool to increase accuracy and decrease testing time when investigating attention development, improving the efficiency of using the FSP as an early diagnostic tool and a surrogate outcome measure.

2.1.2 Difficulties with the eye-tracking measure

A difficulty with eye tracking is the common signal loss in young infants leading to missing data. Eye-movements of infants older than 6 months can easily be tracked by an eye-tracker. However younger infants are more difficult to test because problems occur concerning the accuracy of the eye-tracker and the usability in young subject groups (e.g. Morgante et al., 2012). Firstly, the eye tracker signal with young infants is frequently lost, probably due to the highly reflective retina of very young infants. In pilot studies, several methods were introduced to improve data quality in infants, including the use of neutral density filters covering the sensors of the eye-tracker to reduce the intensity of the pupil image, adjusting the lighting conditions in the room, and adjusting the seating position of the infant so that the camera views the infant’s eyes

from a lower angle than usual, which was found from empirical experimentation improves signal strength. A combination of these methods could successfully improve the eye tracking signal in young infants. Secondly, to guarantee spatial accuracy of the data collected with eye-trackers, a calibration routine should be completed before the experiment (e.g. Bronson, 1990; Gredebäck et al., 2009). However, infants' attention span is shorter than adults'. Therefore, only a shorter calibration routine can be used in young infants, often leading to inaccurate spatial resolution. Pilot studies showed that a greater spatial accuracy was achieved if the eye-tracker was calibrated on an adult subject and this adult calibration was used throughout infant testing; instead of individually calibrating the eye tracker on each infant (see section 2.2.2 for details), as the signal was sometimes lost during calibrations on infant subject. Table 2.1 provides an overview of advantages and disadvantages of different methods. In Chapter 3 eye-tracking with this approach was used to record saccadic shifts in infants in the Fixation Shift Paradigm.

Table 2.1. *Summary of advantages and disadvantages of different methods for saccade investigations.*

Method	**Advantages**	**Disadvantages**
Adult observer	- No equipment required	- Limited temporal resolution - Only post hoc analysis possible - Limited spatial resolution - Need for observer training
Video-coding	- Temporal accuracy	- Time consuming - Only post hoc analysis possible - Limited spatial resolution
Eye tracking	- Temporal accuracy - Higher spatial accuracy - Automatized - No operator/ coder training required - Real-time data access during experiment allows control	- Equipment & software required - Data signal loss

2.1.3 Electroencephalography

Electroencephalography (EEG) measures the distribution of potential changes over time on the cortex through electrodes that are attached to the head of a subject (e.g. Luck, 2005; Regan, 1977, 1989; Shah et al., 2004). Since potentials spread across the head, both local cortical activity close to the electrode and other brain activity from more distant locations are combined at a single electrode. The temporal resolution of EEG is high, allowing a detection of changes in brain potentials within milliseconds (e.g. Luck, 2005; Nunez & Srinivasan, 2006). This temporal accuracy is a particular advantage for measuring neural mechanisms of overt attention shifts, because the high temporal resolution allows the short time window before saccade onset to be easily extracted. Furthermore it allows an investigation of different stages during attention shifts as the high temporal resolution can be used to distinguish temporally separate responses.

Different techniques can be used to analyse cortical signals (see Regan, 1989 for an overview). One method to investigate changes in the quantified voltage over time is to stimulate the system and examine the potential changes in the interval following a stimulus onset, the so-called *transient event-related potentials* (tERPs). As there is an interval between successive stimuli in which the brain can return to a resting state, the brain is in a "resting state" before the occurrence of the stimulus. When the signals are averaged and time-referenced to the repeated stimulus events, they can be related to the appearance of a target stimulus (Regan, 1977, 1989). The brain response to the stimulus (Event-related potential, ERP) can be quantified by local minima and maxima (peaks) and their latencies (Luck, 2005; Regan, 1977, 1989). Several different responses with local peaks can be distinguished in human subjects (Luck, 2005), see section 2.3.3 for an overview. Peak polarities, latencies and amplitudes depend on the task (Regan, 1989) and the age of subjects (e.g. Odom et al., 2010), making it challenging to label them as these components, especially in young children and infants. EEG is a particularly suitable method for testing developing populations (DeBoer, Scott, & Nelson, 2007; M. H. Johnson et al., 2001; Luck & Kappenman, 2011; Thomas & Casey, 2003) and brain development can be linked to behavioural development (de Haan & Johnson, 2003a). Furthermore, EEG can be used to compare clinical groups with typically developing infants, as symptomatic differences are often reflected in brain responses (Thomas & Casey, 2003).

2.1.4 Combining eye-tracking and EEG

EEG, like other functional neuroimaging methods, is susceptible to noise caused by eye-movements or motion artefacts as the intrinsic electrical polarity of the eyes causes potential changes when they move, which overlap with the evoked potentials from the brain (Corby & Kopell, 1972; Croft & Barry, 2000; Joyce, Gorodnitsky, & Kutas, 2004; Luck, 2005). Therefore, research combining eye-tracking and EEG is rare. However, there are several advantages to simultaneously using eye-tracking and EEG. Firstly, eye-tracking data can be monitored during trials to ensure that the subjects are fixating on the required screen locations. This allows an exact determination of whether subjects are fixating stimuli and thereby permits precise control of the visual input, for example by only presenting stimuli when subjects are fixating on the correct location on the screen. Secondly, the temporal co-registration of data makes it possible to use eye-tracking data to determine the time-course of saccades that cause artefacts in EEG data and to reject the affected trials more effectively. In this thesis, eye-tracking data was used to determine trials in which an eye movement occurred during the time window for which the EEG signal was being analysed and exclude them from the analysis to avoid confounding of the data.

To avoid artefacts, previous studies on brain responses related to covert attention mainly used instructions to encourage adult participants to suppress eye-movements (e.g. Anllo-Vento & Hillyard, 1996; Eimer, Forster, Velzen, & Prabhu, 2005; Eimer, Van Velzen, & Driver, 2002; Martinez et al., 1999; Praamstra & Oostenveld, 2003; Shomstein, Kravitz, & Behrmann, 2012; Yamaguchi, Tsuchiya, & Kobayashi, 1994, 1995). It has been suggested that the suppression of eye-movements might elicit potentially less natural brain responses in human subjects than natural attention shifts involving eye movements (Perry & Zeki, 2000), so the combination of eye-tracking and EEG allows research in a more natural setting. Chapter 4 of this thesis will address whether there are significant differences in brain responses between eye-movements and manual responses made to the target without eye movements (because the subject is fixating centrally and the target appears in the periphery), i.e. between overt and covert shifts of attention.

2.2 Method of this thesis

In this thesis stimuli and tasks were kept as similar as possible for adults and infants to avoid ERP differences due to task differences. A use of the same method for infants and adults makes a detection of similar components more reliable, as ERP responses related to similar functions can be determined by investigating which responses show similar effects of conditions (e.g. de Haan, 2007a). This section will summarize the methods that were generally used for recording and processing of eye-tracking data and EEG data, unless specified otherwise in the description of a particular experiment.

2.2.1 Stimuli and equipment

A DELL computer with Linux operating system (Linux Mint 14), with MATLAB (version 7.11.0 (R2010b)) as the presentation program, was used to generate stimuli and present them on a 21.5-inch (54 cm) LCD monitor (Samsung) that extended over 35.8 ° x 22.8 ° of visual angle, running at a frame rate of 60 Hz. Stimuli were presented against a grey background with a mean luminance of 77 cd/m^2. The average viewing distance was 65 cm, which approximates the distance at which the eye-tracker receives the best signal. This position was adjusted until the best possible eye-tracking signal was acquired. Stimulus sizes specified in visual angle are based on this distance (*Figure 2.1*). White curtains were installed around the screen to avoid distraction from the visual stimuli by the surrounding equipment. *Figure 2.1* shows a picture of the set up and equipment used for testing.

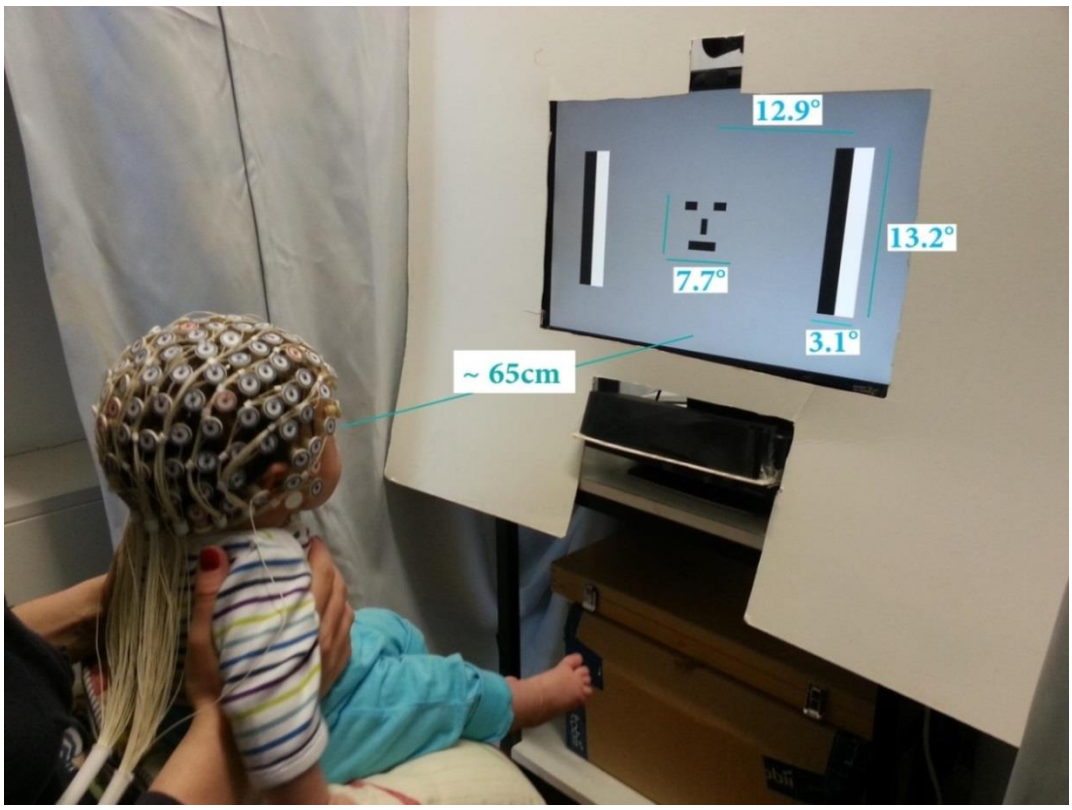


Figure 2.1. Set up used throughout the thesis. Stimuli are presented in black and white against a grey background. The areas behind the screen are covered by cardboard and curtains. The eye-tracker (positioned underneath the screen) monitors the subject's gaze while a Geodesic Sensor Net (positioned on the subject's head) records EEG.

Stimuli differed between the studies but were based on the Fixation Shift Paradigm and stimulus parameters used by Hood and Atkinson (1993) to allow for comparison with previous research. The main differences between the current stimuli and the ones previously used are the eccentricity of peripheral targets (23° in Hood and Atkinson (1993) compared to 12.9 ° in this thesis) and the size (12 ° x 32 ° in Hood and Atkinson (1993) compared to 3.1 ° x 13.2 ° in this thesis). This was necessary because of the smaller monitor and the need to work at a greater viewing distance than Hood and Atkinson (1993) to ensure an optimal signal for the eye tracker. Previous comparisons of different stimuli in the FSP indicate that stimulus features are not crucial for the results in regard to attention disengagement (Atkinson et al., 1992; Hood & Atkinson, 1993), although maternal faces can lead to different saccade latencies (Hunnius & Geuze, 2004). An eye tracking study carried out on adult subjects (Appendix B) confirmed that stimulus size and eccentricity had no significant effect on saccade latencies in the paradigm used throughout this thesis. The peripheral stimuli were well above the acuity and contrast sensitivity limit of infants in the first year of life and so

were easily visible to all typically developing infants in these studies (e.g. Atkinson, 2000b; Coch & Gullick, 2011; Courage & Adams, 1990; Jones, Kalwarowsky, Atkinson, Braddick, & Nardini, 2014; Mayer et al., 1995; Salomao & Ventura, 1995; Teller, McDonald, Preston, Sebris, & Dobson, 1986). They changed colour at a rate of 3 reversals per second. A central stimulus appeared for a randomised inter-trial interval between 0.5 and 2.5 seconds before peripheral targets occurred. This interval is suitable for infants as well as adults, as infant ERPs can last longer; meaning that more time should be left between trials to avoid an overlap of responses. *Figure 2.2* shows examples of the stimulus displays used in these studies.

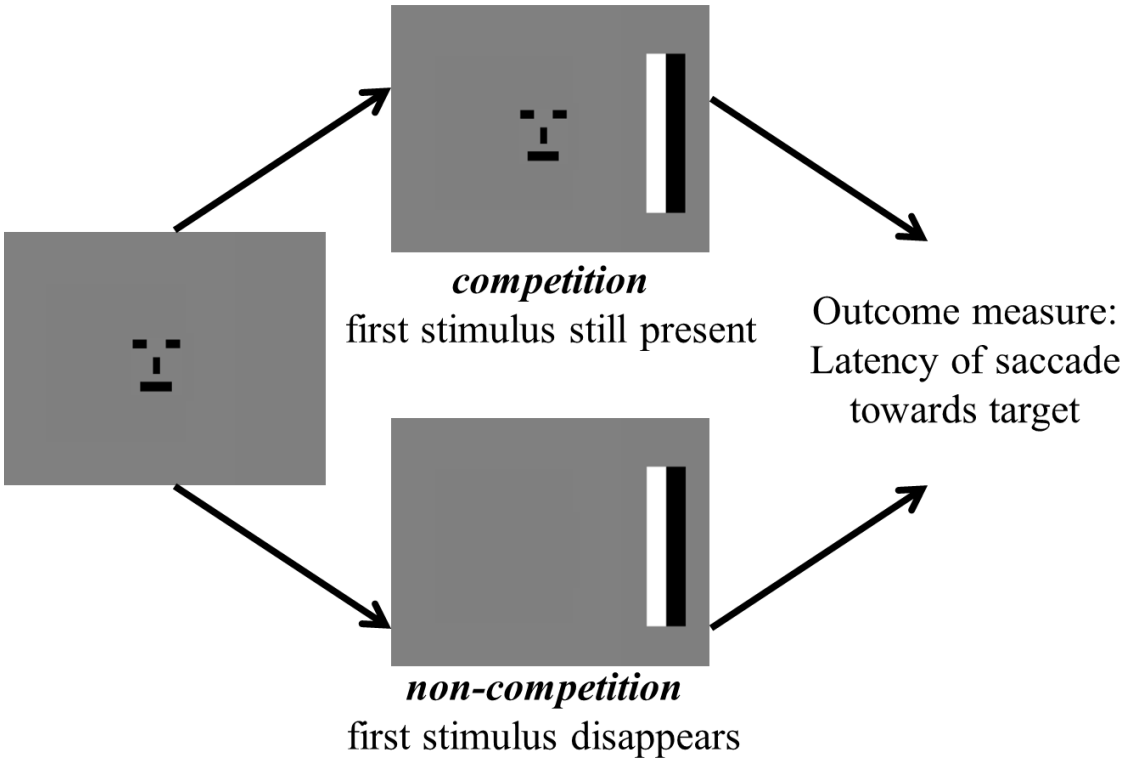


Figure 2.2. Example display of some of the stimuli used in this thesis. A central stimulus appears and if it is fixated, peripheral target stimuli automatically appear on either side of the screen until the subject makes a saccade towards them.

2.2.2 Eye -Tracking

A remote eye-tracker, Tobii X120, was used to record the gaze-position of subjects during the experiment. At the start of each experiment, the eye-tracking system was calibrated using a five point routine that took less than 2 minutes to complete. The routine consisted of a 1.8° white dot appearing in the centre of the screen and moving to each of the corners of the screen (*Figure 2.3*). For adult subjects this calibration was

performed by each individual subject, whereas for infant subjects the calibration was performed on an adult before the experiment began. Pilot studies on infants of different ages showed that a calibration on an adult led to cleaner data and less data loss than attempting to calibrate the eye tracker on individual infants, which led to inaccurate calibrations and data loss[1]. As the stimuli were big and did not require high spatial accuracy, the adult calibration resulted in more accurate measures. The eye tracker sampled the subjects' eye positions at a rate of 60 Hz. The sequence of gaze position within each trial was saved for further analysis.

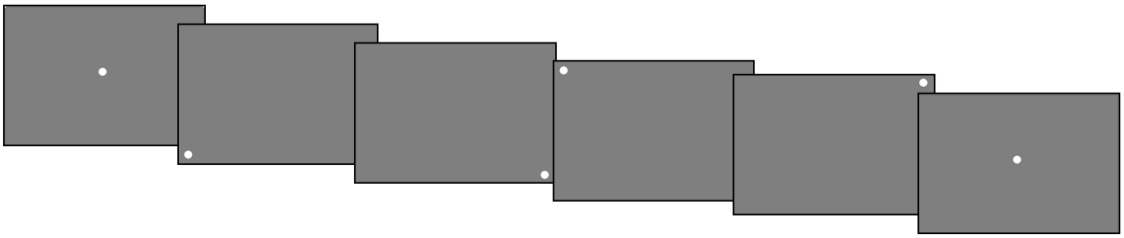


Figure 2.3. Calibration routine order. The white dot slowly moves from the centre to the bottom left, bottom right, top left and top right corner of the screen and back to the centre.

2.2.3 Online analysis of eye-tracking data

During the experiment the eye-tracking data was accessed to monitor gaze positions. Whether a subject fixated on the initially presented central stimulus was determined by calculating the dispersion of measured gaze position from the centre of the fixated object at the end of the random inter-trial interval. When this dispersion was less than 2.64 degree of visual angle for adults or less than 5.1 degree for infants (note that this criterion is slightly higher than the actual size of the target, to allow for noise in eye-tracking data, but still avoids an overlap of regions of interest between stimuli) for at least 20 samples (~330 ms), target stimuli appeared in the periphery. If the subject looked at a peripheral stimulus, defined as the measured gaze position being in the area around the target stimulus for more than 20 samples (~330 ms), the stimulus automatically disappeared and the next trial began.

[1] To ensure more comparable conditions, the calibration was carried out on an adult with bright blue eyes, as their features are more similar to the infant eyes in these studies (Gredebäck et al., 2009).

2.2.4 Post experimental analysis

After completing the experiment, the eye-tracking data was processed for all samples and analysed for each trial. The analysis of eye-tracking data was programmed using MATLAB (version 7.14.0.739, R2012a, 64bit). If eye-position data was missing in a sample, the data in this sample was interpolated with the average of the previous sample and the first subsequent successful sample. If several successive samples were missing this procedure was repeated for all of them. The onset of a saccade was defined as the time point before a horizontal change of gaze-position on the screen by more than 2.2 degree of visual angle between two successive samples (i.e. a velocity higher than 132 degree per second).

Trials involving noisy eye tracking data were excluded according to the following criteria: (1) if the gaze position at the onset of the second stimulus was not on the screen (approximated as 19.64 x 10.98 degrees from centre of screen), indicating that the subject did not fixate the screen or that the eye tracker lost the signal, (2) if the trial contained too many excursions in fixation position (> 20% of samples differed by more than 2.2 degree of visual angle from the previous sample) indicating fuzziness or signal-loss from the eye-tracker, or (3) if the first saccade occurred earlier than 0.1 seconds after the appearance of the peripheral target, as it is very unlikely that those saccades were related to the appearance of the target and so were probably anticipatory saccades or unrelated to the stimulus (cf. Gomez, Atienza, Gomez, & Vazquez, 1996).

Trials in which the first saccade occurred later than 5 seconds after target onset were registered as a ‘sticky fixations’ and excluded from the analysis of latencies. Although some previous studies on older infants around 6 months used lower cut-off values for sticky fixations (e.g. 1 sec, Csibra et al., 1998), previous studies demonstrate that especially young infants between 1 and 3 months frequently refixate after a longer time interval (e.g. Atkinson et al., 1992; Hood & Atkinson, 1993; Matsuzawa & Shimojo, 1997), suggesting that they do not simply get “stuck” on the stimulus but need additional time to shift towards it. To allow for these delayed saccades, all refixations within 5 sec after target onset were still considered correct refixations as they reflect a delay rather than an inability to shift. Trials with the initial saccade to the wrong direction were registered as “misdirected saccades” and excluded from the analysis; it was investigated whether they were subsequently corrected towards the valid direction. For valid trials with the first saccade towards the correct direction, the latency

(difference in time between target onset and onset of the first lateral saccade towards it) was calculated and averaged across the condition. The gaze position (in degrees of visual angle from the centre of the screen) after the first saccade was calculated by averaging across samples after the first saccade towards the correct direction either until the next saccade occurred away from the fixation position or for a maximum of 10 samples. The total number of sticky fixations, saccades to the wrong direction and noisy trials were calculated.

The eye-tracking data processing can take approximately 30+/-2 ms (Tobii Technology, 2010b) and asynchrony between the eye tracking refresh pulse and the monitor's refresh pulse may lead to an additional delay of up to 16.7 ms (at a rate of 60 Hz), on average 8.3 ms. The raw eye-tracking latencies were used for comparisons between conditions, and so a fairly constant delay should not affect differences between them, but the absolute latencies may differ from the measured ones. When excluding premature saccades to clean the EEG data, a strict correction of 50 ms was used, to ensure that no trials containing saccades were included in the EEG analysis.

2.2.5 EEG system

In experiments in Chapter 4 to 6, while the subjects were engaged in the behavioural tasks, their EEG activity was recorded using Electrical Geodesics Inc. NetAmp300 amplifier[2] and 128- channel Ag/AgCl electrode nets (Tucker, 1993). EEG was recorded on a separate computer (Macintosh) using Net Station 4.2 (© 1994-2006, Electrical Geodesics, Inc.). Electrode impedance was adjusted to less than 90 kΩ, with the majority of electrodes having an impedance of less than 40 kΩ. Ferree, Luu, Russell, and Tucker (2001) showed that an increase of impedance had a negligible effect on EEG data quality in their tests up to 40 kΩ and Richards (2005) argues that a use of up to 100 kΩ impedance only leads to less than 0.05% data loss according to the calculations of Ferree et al. (2001), making this value more feasible for infant research. Samples were collected at a rate of 250 Hz, which is slightly higher than the recommended rate for infant populations (DeBoer et al., 2007), therefore allowing higher temporal accuracy.

[2] The NetAmp300 Amplifier from EGI automatically applies an analogue low-pass filter at 6 kHz and after the analogue-digital conversion of the data applies a 4 kHz low-pass filter. These filters should not affect the data at a sampling rate of 250 Hz used in this thesis. No further online HP or LP filters were applied during data recording to avoid data distortion.

2.3 EEG analysis

Careful considerations need to be taken for processing of EEG data that contains regular saccades, as in overt attention shift tasks in this thesis. To avoid distortions of EEG data due to eye movements, short ERP epochs were extracted in this thesis that ended before the onset of saccades determined by the eye tracker. To ensure that trials with particularly early eye movements would not distort the findings, care was also taken to exclude trials in which a saccade occurred less than 50 ms after the end of the EEG analysis window due to the abovementioned eye tracking data delay. An alternative possibility to avoid confounding the data with eye artefacts would be to use independent component analysis (ICA) to identify eye movement components in the EEG data and exclude them from the analysis (e.g. Jung et al., 1998). However, the visual input to the brain changes during saccadic eye movements, possibly eliciting new visual responses. As this study investigated visual attention, only ERPs prior to saccade execution were analysed, to avoid confounds both with overlapping visual signals and with eye movement artefacts. This ensures that the extracted epochs are free of eye movement artefacts.

However, filtering is carried out on the raw signal before extraction of the time segment preceding the saccade on each trial. Filters can lead to smeared responses occurring before the actual response of opposite polarity (e.g. Luck, 2005; Tanner, Morgan-Short, & Luck, 2015). An experimental comparison of different filter settings on a dataset containing regular eye-movements showed that artefacts arising from the saccades could be intruding into the analysed section of the EEG. Appendix C presents data exploring these possible artefacts and the effect of applying different filters. It was concluded that the contribution of saccade artefacts could be excluded by applying a high pass filter at 0.01 Hz in the adult records and 0.1 Hz for infant records. Because drift artefacts are more likely in infants 0.1 Hz is a commonly used high pass filter cut off (Hoehl & Wahl, 2012). With these precautions, it is possible to be confident that the measured waveforms represent brain activity preceding the saccade without significant intrusion of eye movement artefacts.

The timing of the EEG system was measured to ensure that triggers were aligned with visual events (Appendix D) and the data timing was corrected by subtracting the detected delay. The data was average referenced using all electrodes except for the outer frontal electrodes that are prone to noise (i.e. excluding Geodesic Sensor Net electrodes

1, 8, 14, 17, 21, 25, 32, 38, 43, 48, 49, 113, 119, 120, 121, 125, 126, 127, 128). The EEG data analysis was programmed in MATLAB, using the following steps:

1) Butterworth filters were used firstly for notch filtering around the line noise frequency [49 to 51 Hz], secondly for high-pass filtering (cut off: 0.01 Hz for adults, 0.1 Hz for infants) and thirdly for low-pass filtering (cut off: 25 Hz).

2) Segmentation of data into epochs of -200 to 180 ms around target onset for adults or -200 to 230 ms around target onset for infants.

3) Noisy epochs and electrodes were then determined by using the median absolute deviation about the median (MAD)(Hampel, 1974), as this is a measure that is fairly robust to noise (Hampel, 1974; Leys, Ley, Klein, Bernard, & Licata, 2013; Rousseeuw & Croux, 1993). Using a threshold[3] of 3*MAD*1.483, values that showed higher deviations than this threshold were excluded from further analyses as "noisy trials". Epochs were included if the following criteria were within this threshold calculated using the individual data in more than 70 channels: (a) SD over samples per trial, (b) range of amplitude between minimum and maximum amplitude value within epoch, (c) drift (difference in amplitude between the average period before and after target onset), (d) Maximum steps in data amplitude between successive samples; and if (e) the SD over samples per trial was bigger than 0.1 (i.e. the electrode received a signal).

4) Other epochs were interpolated using spherical spline interpolation, and only those that were acceptable after interpolation were used for further analysis.

5) Finally, the average voltage during the baseline period ([-200; 0] ms before target onset) was used to correct the data from target onset onwards, individually for each trial and electrode. Scalp surface maps were created using spherical spline interpolation.

2.3.1 ERP measures

Event-related potentials (ERPs) are commonly quantified by the peaks and latencies of positive and negative waves in the brain response to the target stimulus, although the peaks do not necessary reflect the underlying component or neural process (Luck, 2005; Luck & Kappenman, 2011; Regan, 1989). Different methods can be used

[3] 1.483 is the standard constant for calculation of MAD thresholds suggested by Leys et al. (2013)

to quantify responses and, as they have different advantages and disadvantages, multiple measures were used in this thesis to combine the advantages of all methods.

To quantify the *magnitude* of a response, peak amplitude, local peak amplitude and mean amplitude measures are commonly used (Luck, 2005; Regan, 1989). The peak amplitude measure involves extracting the maximum or minimum value of a response in a specific time window. It has been used very commonly in other studies (e.g. Harter et al., 1982; Mangun, 1995; Rugg et al., 1987; Slavutskaya, Moiseeva, Kotenev, Karelin, & Shulgovskiy, 2014), and is therefore analysed in this thesis to allow for comparability with previous research. However, this analysis is prone to distortion due to high-frequency noise (Luck, 2005). Furthermore, the extraction of peaks within a limited time window restricts the range of responses, as a maximum peak may lie outside the time window, leading to floor and ceiling effects. There is furthermore a possibility of later responses overlapping with the response of interest, increasing the probability of maxima being detected at the upper or lower limit of the extracted time window. The calculation of a local peak (local maximum that is surrounded by smaller values) excludes the possibility of floor and ceiling effects. To allow for effects of high-frequency noise, mean amplitude within a certain time window can be calculated (Caldara et al., 2004; Heinze et al., 1990; Luck, 2005; Luck et al., 1990; Praamstra & Oostenveld, 2003; Regan, 1989). This method is particularly suitable for responses with different polarities at different scalp sites (e.g. ipsilateral and contralateral) and for data containing significant amounts of high-frequency noise. However, the results with this method depend on the time window used for analysis. Due to their different advantages, different methods were used to investigate infants and adult responses. Adult data, which contains clear peaks and relatively little noise, was analysed by extracting peak amplitudes for each condition in a defined time window on an individual subject basis. This method allows for a detailed analysis of amplitudes of different response peaks within a short time window. It furthermore simplifies the comparison with previous studies using the same measures with adult subjects. Infant data contains more extreme excursions due to noise; hence, mean amplitudes were calculated within subsequent time windows to avoid distortions due to noisy data. This method has been used in previous infant studies on attention as well (e.g. Csibra et al., 1998) and therefore allows for a comparison of results.

To quantify the *latency* of a response, different methods can be used. Peak latency and local peak latency measures were used in many previous studies on adult subjects (e.g. Harter et al., 1982; Mangun, 1995; Rugg et al., 1987; Slavutskaya et al., 2014) and were therefore calculated for comparability in studies on adults in this thesis. A different measure, the fractional area latency, uses the area under the ERP curve to calculate the latency at which the area is split in half, indicating that the response peaked (Luck, 2005). This measure strongly depends on the time window that is used for analyses and as the variability in infant subjects is high, time-window dependent measures can be distorted in young populations. Therefore, this thesis focused on peak latency measures instead of fractional area latencies in adult subjects. Peak latencies were determined on an individual subject level separately for each condition. As latency measures are prone to noise they were not calculated in infants subjects. Instead, mean amplitudes were calculated in 50 ms time windows within the extracted window, to monitor the time course of the observed responses. Peaks and latencies can be compared between different conditions.

For statistical analyses, linear mixed effects models, with random intercepts but fixed slopes across participants were used. As missing data is common in infant studies, linear mixed models were used to account for missing data, unequal trial numbers between subjects and variability across participants (e.g. DeBoer et al., 2007; McLean, Sanders, & Stroup, 1991). This procedure allows for random individual variations (Laird & Ware, 1982) by treating participants as a random effects factor in the analysis. For consistency, the same statistics were calculated for infants and adults. Effect sizes (Cohen's d) of significant main effects were estimated from mean values and standard deviations. For binary outcome variable, mixed logistic regressions were computed. Mixed linear models were calculated using SPSS (IBM Corp, 2011) and mixed effect logistic regressions were calculated using R (Core Team, 2012). Both types of models were used to calculate main effects and interaction effects of all independent variables on the dependent variables. To further explore interaction effects, descriptive statistics were reported and plots with 95% confidence intervals were used to visualise the directions of the effects.

2.3.2 Adult ERPs

From reviewing previous literature, different ERPs can be expected in response to the stimuli used in this thesis. Two different attentional mechanisms can be studied

with EEG, (1) the modulation related to attention of common ERP responses to stimuli and (2) the occurrence and timing of responses involved in covert and overt shifts of attention, that correspond to the three stages of disengagement, shift and engagement. This section reviews the responses that were expected in adult participants, focusing on the time window between target onset and 180 ms (the window that can be extracted before saccade onset), and elaborates on the reasons for choosing the time windows that were extracted. To allow for comparability between studies the same time windows were extracted for all adult data.

Visual responses

Visual stimuli usually evoke a series of responses located in posterior areas of the scalp (e.g. Harter et al., 1982; Heinze et al., 1990; Luck, 2005; Luck et al., 1990; Mangun, Hopfinger, Kussmaul, Fletcher, & Heinze, 1997), in particular around the electrodes O1 and O2 in the 10-10 system (e.g. Boksem, Meijman, & Lorist, 2005; Csibra et al., 1997; Mangun, 1995; Mangun et al., 1997). The Geodesic Sensor Net has a higher density of electrodes across the scalp compared to most commonly used gel-based EEG systems. Averaging across several electrodes can decrease noise, which is especially beneficial for infant data (e.g. Richards, 2001b), improving data quality. For this thesis, the series of posterior responses was extracted in two posterior lateral clusters including electrodes (65, 66, 70, 71, 69, 74) in the left hemisphere and electrodes (90, 84, 76, 83, 82, 89) in the right hemisphere (*Figure 2.4*). These electrodes are located symmetrically around the corresponding electrodes O1 and O2 in the 10-10 system that have been found to reliably show visual responses in previous studies (e.g. Boksem et al., 2005; Csibra et al., 1997; Mangun, 1995; Mangun et al., 1997).

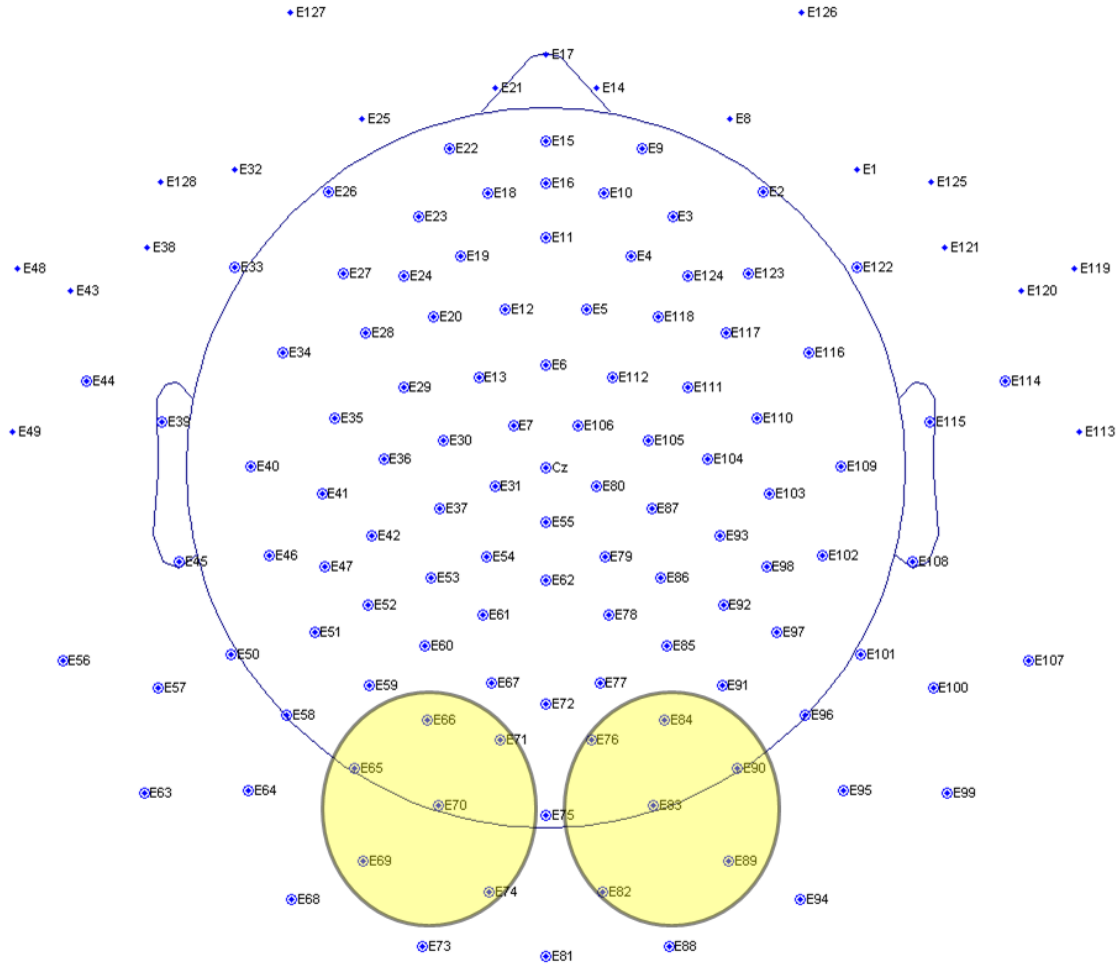


Figure 2.4. Posterior electrode cluster extracted for the analysis.

In adult subjects, the first major response to visual stimuli starts at 40 – 60 ms and peaks between 80 and 100 ms in posterior midline areas (C1). It is followed by a positive deflection often labelled as P1 with an onset between 60 and 90 ms and peaking around 100-130 ms (Luck, 2005). These early responses sometimes overlap due to their temporal proximity and because their sources lie close to each other. Other studies hypothesise that two responses are visible because of an overlap of the P1 with a "notching" negativity around 130 ms (Luck & Kappenman, 2011). In some studies two posterior responses could be split depending on their location into an initial contralateral positivity, and a later ipsilateral one (Csibra et al., 1997; Mangun, 1995).

The earlier posterior positivity was determined in a time window between 40 (earliest onset suggested by Luck (2005)) and 90 ms (to avoid an overlap with the subsequent response) after target onset.

Csibra et al. (1997) found the later posterior peak in a time window at the end of their extracted ERP window (128-148 ms). Considering previous research identifying the peak between 100 ms and 250 ms (Boksem et al., 2005; Harter et al., 1982; Heinze et al., 1990; Luck et al., 1990; Praamstra & Oostenveld, 2003), peak amplitudes and latencies were calculated in the time window from 100 ms (to avoid overlap with the earlier contralateral P1) to 180 ms (end of the time window extractable before saccade onset).

Attentional responses

Attention modulates visual responses and shows additional attentional responses (review: Chapter 1, section 1.4). Previous verbal measures of attention in adults show that, in general, the effects of attention include a selection of the target, which is supported by excitatory mechanisms, and a suppression of distractors, supported by inhibitory mechanisms in the brain (Humphreys et al., 2009; Kastner & Ungerleider, 2000). Most studies of visual attention found effects on a P1-N1 complex with a posterior positivity peaking between 110 and 250 ms (Harter et al., 1982; Heinze et al., 1990; Luck et al., 1990; Mangun, 1995; Rugg et al., 1987) followed by a negativity peaking between 150 and 180 ms (Harter et al., 1982; Rugg et al., 1987). These components are often lateralised (Heinze et al., 1990; Luck et al., 1990; Mangun, 1995; Rugg et al., 1987) and peak in contralateral regions before ipsilateral regions (Rugg et al., 1987). The posterior responses are enhanced by attention (Harter et al., 1982; Heinze et al., 1990; Luck et al., 1990; Mangun, 1995; Rugg et al., 1987), especially in the contralateral hemisphere (Harter et al., 1982). As reviewed in Chapter 1, visual responses are greater when only one stimulus is visible than when other distractors are simultaneously presented (e.g. Keitel et al., 2013; Moran & Desimone, 1985). Attention modulation of P1 might reflect an early facilitation of sensory processing, whereas modulation of N1 relates to an orienting of attention towards a specific location (e.g. Heinze et al., 1990; Luck et al., 1990).

Frontal negativity

An early frontal negativity has been found to be influenced by spatial attention (e.g. Harter et al., 1982; Heinze et al., 1990; Rugg et al., 1987). It typically peaks in central and frontal sites, having higher amplitudes in the contralateral hemisphere (Heinze et al., 1990; Rugg et al., 1987). The latency of this response can vary depending

on electrode site (e.g. between 147 ms and 171 ms (Rugg et al., 1987), and 150-200 ms in fronto-central areas (Heinze et al., 1990)). In this study the peak of this response was extracted in the window between 100 and 180 ms. A symmetrical area including frontal and fronto-central electrodes was extracted over the electrodes [12, 13, 19, 24, 20, 28, 29] in the left hemisphere and the electrodes [4, 5, 111, 112, 117, 118, 124] in the right, *Figure 2.5*. Peaks and latencies were determined in the time window from [100; 180] ms.

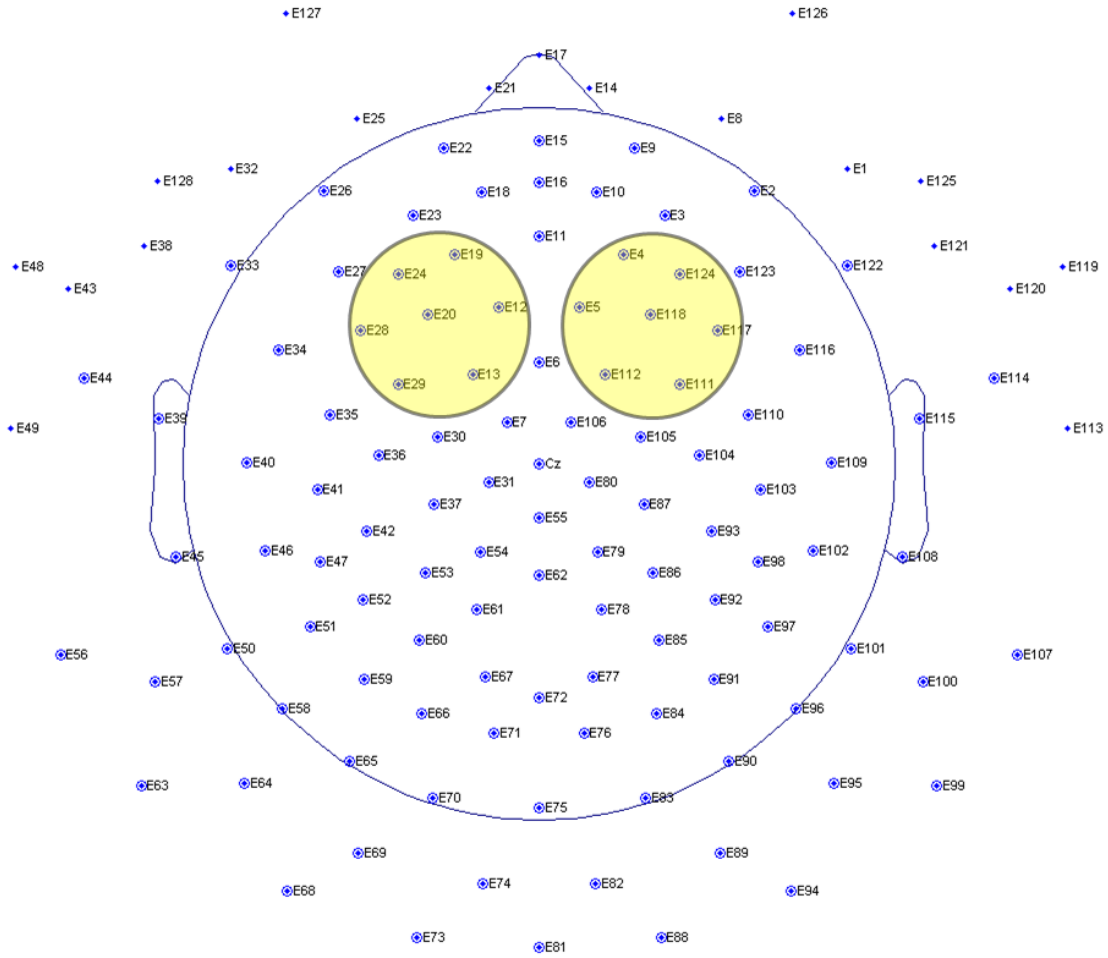


Figure 2.5. Frontal electrode cluster extracted for analyses.

Preparation of saccades

Saccades can be preceded by responses in anterior regions of the brain. Foxe and Simpson (2002) described frontal activation to occur very early after stimulus onset. They found a complex of negativity 50-62 ms after target onset at POz, a positivity 62-80 ms after target onset in PO3 and PO4 and a negativity after 80 ms in P03. At 70 ms a

negativity occurs in CPz. Slavutskaya et al. (2014) found two positive peaks occurring 109-120 ms and 150-250 ms after target onset in frontal, central and parietal areas.

It is possible that anterior activation stems from the frontal eye-fields which have been found to be involved in saccade preparation (e.g. Guitton et al., 1985; Henik et al., 1994; Miller, 2000; Neggers et al., 2005; Peelen et al., 2004; Pierrot-Deseilligny, Rivaud, et al., 1991; Rafal et al., 2000). The frontal eye-fields are located in the middle frontal gyrus, between Brodmann area 8, 9 and 6 (review: Crowne, 1983; Paus, 1996) and ERP responses from these areas can be extracted close to the electrodes FC3 and FC4 in the 10-10 system (Brainmaster Technologies, 2014). FEF responses were found to occur early, between 45 ms after target onset in intracerebral recordings in epilepsy patients (Kirchner et al., 2009) and 100 ms (foveal stimuli) to 200-300 ms (foveal and extrafoveal stimuli) after stimulus onset and are more pronounced in the contralateral brain hemisphere (Blanke et al., 1999). Possible responses in these areas were explored by visual inspection of topographical plots. Table 2.2 summarises the responses that were extracted in adult subjects throughout this thesis.

Table 2.2. *Summary of the responses that were extracted in all adult studies for this thesis, the electrode locations, the time windows in which the peak amplitude and latency was calculated.*

Response	Electrode location	Time window (peak)
Early occipital positivity	Lateral occipital	40 – 90 ms
Late occipital positivity	Lateral occipital	100 – 180 ms
Frontal negativity	Lateral frontal	100 – 180 ms

2.3.3 Infant ERPs

An advantage of the EEG is that it can readily be used to monitor functional brain development in infants. Visual evoked potentials can be measured in infants from 24 weeks of gestation on (Chin, Taylor, Menzies, & Whyte, 1985), and are being used in many different contexts, for example to estimate contrast sensitivity and visual acuity (e.g. Atkinson, Braddick, & French, 1979; Fiorentini, Pirchio, & Spinelli, 1983; L. Harris, Atkinson, & Braddick, 1976), for identifying the development of particular cortical mechanisms (Braddick et al., 1980; Braddick, Wattam-Bell, & Atkinson, 1986),

or to test for potential brain damage (e.g. Atkinson et al., 2002; Mercuri et al., 1998; Whitham et al., 2010). Simple visual responses and their modulation through attention have widely been studied in infants (e.g. de Haan, 2007b; G. D. Reynolds & Richards, 2005) and adult research shows that attention shifts coincide with increased responses towards the attended stimuli (e.g. Di Russo, Martínez, & Hillyard, 2003; M. M. Müller & Hillyard, 2000). Only few studies have discussed the time course of the stages involved in attention shifts (but see e.g. Csibra et al., 1997; Csibra et al., 1998). This section reviews visual and attentional ERPs commonly observed in infants.

General differences

Brain responses in infants differ considerably from those commonly observed in adults in several different features. Firstly, the number of distinct responses that can be identified significantly increases over age (Barnet et al., 1980). Secondly, the infant visual system is significantly noisier than the adult system (Brown, 1994; Picton & Taylor, 2007). Thirdly, response amplitudes are significantly larger in infants than in adults (Hou, Pettet, Sampath, Candy, & Norcia, 2003; Sokol & Dobson, 1976), with VEP amplitudes increasing in the first 6 months of life and then decreasing until adulthood (Barnet et al., 1980). Furthermore, latencies of VEP amplitudes decrease during infancy (Barnet et al., 1980; Ellingson, Lathrop, Nelson, & Danahy, 1972; McCulloch, 2007; McCulloch & Skarf, 1991; Nelson & McCleery, 2008). From approximately 220 – 300 ms P1 latency at 1 month they asymptote towards the adult latency of 100 ms at approximately 4 months (Lee, Birtles, Wattam-Bell, Atkinson, & Braddick, 2012a, 2012b; McCulloch, 2007; McCulloch & Skarf, 1991; Nelson & McCleery, 2008). This indicates that the peaks of responses can be delayed by as much as 200 ms in early infancy. Tsuneishi and Casaer (1997) note that this decrease does not follow a linear pattern, but rather decreases step wise by up to 6 ms per week, which may be due to stepwise myelination (Dubois et al., 2008). Finally, elicited responses vary greatly between individuals of the same age (Barnet et al., 1980; Coch & Gullick, 2011; Eeg-Olofsson, 1980; Ellingson, 1970; Ellingson et al., 1972; McCulloch, 2007; McCulloch & Skarf, 1991; Nelson & McCleery, 2008; Pryds, Trojaborg, Carlsen, & Jensen, 1989). In the studies within this thesis a wide age range of infants between 1 and 8 months of age were tested, with considerable variation in latencies expected across individuals and ages. To allow for this variation between individuals, only small age ranges of between 1 and 2 months should be averaged across in infants (DeBoer et

al., 2007; Picton et al., 2000). Therefore, EEG data was analysed in age groups that varied by less than 1 month in young infants (age groups: 1.5-2.5 months, 2.5-3.5 months) and less than 2 months in older infants in this thesis (age groups: 3.5-5.5 months and 5.5- 7.5 months, see Chapter 6). Furthermore, mean amplitudes were calculated, as they are less prone to noise than peak amplitudes. To investigate the time course of responses, amplitudes were averaged across subsequent time intervals of 50 ms and the time window was included as a factor in the analysis, to monitor changes in amplitude over time.

Changes in the number of ERP peaks and their latency make it difficult to directly compare them with the responses commonly found in adult subjects. Responses to the same stimuli may differ in latency, amplitude, polarity and location between adults and infants (review: de Haan, 2007a), and different brain regions may be involved in the same behavioural processes at different ages, as suggested by lesion studies in primates (Malkova, Bachevalier, Webster, & Mishkin, 2000) and human children (Bates, Vicari, & Trauner, 1999). It is thus unclear whether the responses identified in infants and adults have the same underlying neural mechanisms or whether they reflect different components that disappear or develop with age (de Haan, 2007a, 2007b). The following sections summarize the brain responses that are commonly observed in infants.

Visual responses

Several early visual responses have been identified in posterior areas of the scalp in infants, probably originating in the visual cortex outside V1 (extrastriate occipital cortex) (e.g. Richards, 2005). In the current thesis, these responses were extracted at the same electrode locations as in adults (see Figures 2.4 and 2.5 above). Although brain responses to simple flashes of light might be mature by 4 months of age, responses to more complex stimuli like checkerboards are developing throughout childhood (e.g. Coch & Gullick, 2011). The ontogenetically first response that appears in response to visual stimulation is a negativity occurring around approximately 300 ms after stimulation onset in posterior regions (Benavente, Tamargo, Tajada, Yuste, & Oliván, 2005; Crognale, Kelly, Chang, Weiss, & Teller, 1997; Ferriss, Davis, Dorsen, & Hackett, 1967; McCulloch, 2007; Pryds et al., 1989). This response has been termed N3 due to its peak latency of around 300 ms at birth (McCulloch, 2007) or N1 as it is the first negativity visible in young infants (Pryds et al., 1989). Different studies found the

response latency varying between 100 (Crognale et al., 1997) and 381 (Ferriss et al., 1967) milliseconds after stimulation onset, depending on the task and age of participants (see Table 2.3 for a summary). Some studies found a negative response to only be present directly after birth and disappear within the first 15 weeks of life (McCulloch, 2007), while others observed it at a later age as well (Crognale et al., 1997; Ferriss et al., 1967), and others suggest that a negativity is only emerging between 2 and 5 months (Regan & Spekreijse, 1986). It is possible that these different studies observe different responses, including the N1 and N3 described by Coch and Gullick (2011).

Table 2.3. *Negative posterior responses in infant subjects.*

Study	**Measure**	**Age group**	**Latency**	**Label of response**
Pryds et al. (1989)	Visual stimulus onset	Preterm infants	234 to 289 ms	N1
Ferriss et al. (1967)	Flash	3 months olds	118-232 ms	N2
		Newborns	up to 381 ms	
Crognale et al. (1997)	Pattern onset	1-2 weeks	200 ms onset	
		3 months	100 ms onset	
Regan and Spekreijse (1986)	Pattern onset	2-5 months	180-350 ms	
Benavente et al. (2005)	Flash	Newborns	145.5 ms	N1
			255.7 ms	N3
Csibra et al. (1998)	Peripheral stimulus onset	6 months	60-140 ms	N100

In older infants the negativity is commonly preceded by a posterior positivity peaking between 100 and 250 ms post stimulation (Benavente et al., 2005; Crognale et al., 1997; de Haan, 2007a; Ferriss et al., 1967; McCulloch, 2007; Regan & Spekreijse, 1986), see Table 2.4 for a summary of the component. This "P2" response can be detected most reliably across ages (Benavente et al., 2005) and the latency significantly decreases with age from 200 ms in the first weeks of life to 100 ms at 3 months and can be traced back to the "P1" positivity found in adults (Coch & Gullick, 2011; Crognale et

al., 1997; Ferriss et al., 1967). Note that the response has been labelled differently across the literature, sometimes referring to the latency in infants (e.g. P2, P200) or relating it to the adult P1. Hence, the notations of these peaks cannot readily be transferred from one study to another with differing paradigms.

Benavente et al. (2005) found the responses to be preceded by another negativity (N1), peaking around 145.5 ms in new-borns, and similarly Csibra et al. (1998) found a negativity between 60 and 140 ms in 6 months old infants.

Table 2.4. *Early positive posterior responses in infant subjects.*

Study	Measure	Age group	Latency	Label of response
Benavente et al. (2005)	Flash	1-6 months	100-200 ms	P2
Ferriss et al. (1967)	Flash	Newborns	219 ms	P2
Crognale et al. (1997)	Pattern onset	1-2 weeks 3 months	200 ms onset 100 ms onset	
Regan and Spekreijse (1986)	Pattern onset	2 months	Approx. 100-250 ms	
Richards (2000, 2005)	Peripheral stimulus onset	14-26 weeks	150 ms	
Csibra et al. (1998)	Peripheral stimulus onset	6 months	100-124 ms	P168

Attentional responses

Attention modulation can affect different ERP responses. Richards (2000, 2005) found attentional modulation in early visual responses in infants during covert attention shifts, as indicated by larger amplitudes of an occipital positivity 150 ms after onset towards validly cued targets than towards invalidly cued targets in infants between 14 and 26 weeks. In contrast to this Csibra et al. (1998) did not find modulations on their

early P1-N1 complex in 6 months old infants between gap and overlap conditions for overt attention shifts. It is therefore unclear whether attentional modulations of earlier posterior responses can be expected in the current thesis.

Other attentional responses can be found in infants; however, they usually appear later than the time window that can be extracted before saccade onset and hence cannot be investigated if the FSP involves eye-movements. The Nc appears between 600 and 1200 ms after target onset in the first year of life and has been related to visual attention and memory (de Haan, 2007b). A central negativity (Nc) 450-550 ms after stimulus onset represents attention to novel stimuli between 4.5 and 7.5 months (Richards, 2003a). It shows greater amplitudes during attention periods, than during periods of low arousal. An early negative slow wave (eNSW) can be observed in fronto-central areas, beginning 100 ms after target onset (ranging between 10 and 900 ms), possibly being involved in attention processes (de Haan, 2007b). Slow wave responses that have been related to attention and memory processes tend to occur in anterior regions, possibly generated by temporal and frontal regions (de Haan, 2007b; G. D. Reynolds & Richards, 2005). As these responses have been found in later time-windows that cannot be extracted in this study due to an overlap with saccade onset, they have not been analysed in the experiments reported here.

Brain responses during overt shifts of attention

Limited research exists on overt attention shifts in adults (Csibra et al., 1997; Moster & Philadethia, 1991) and young infants (Csibra et al., 1998). Due to the high temporal resolution of EEG compared to other neuroimaging methods, it can be used to identify different responses involved in the three stages of attention shifts (disengagement, shift, engagement). A posterior frontal positivity has previously been found to differ between attention shifts in gap and overlap conditions between 80 and 200 ms after target onset (Csibra et al., 1998), suggesting that this early response may reflect disengagement of attention. The response was more pronounced in the left hemisphere and seemed to peak towards the end of the time window they extracted. However, Csibra et al. (1998) did not analyse the response beyond 200 ms to avoid confounds with eye-movement artefacts, leaving the possibility that it might occur even later in younger infants.

In addition to analysing ERPs referred to the target onset, it is also possible to extract the EEG data preceding a saccade, i.e. time referenced to saccade onset, instead of relating the response to the stimulus onset. With this method pre-saccadic potentials can be observed, including a spike potential before saccades in parietal cortex in adults (Csibra et al., 1997), and 12 months olds but not in younger infants (Csibra et al., 1998). These potentials can provide insights into the responses related to the initiation of eye movements. However, the current thesis focused on stimulus-onset linked responses, as previous research suggested that saccade-linked responses only occur in infants older than the ones tested in this thesis (Csibra et al., 1998; Csibra, Tucker, Volein, & Johnson, 2000) and may therefore not be the driving forces behind the differences in the ability to shift attention that were the topic of this thesis.

Chapter 6 combines eye-tracking and EEG with the FSP to further investigate the time course of cortical responses to peripheral targets under competition and non-competition conditions in infants.

2.4 Conclusion

This chapter reviewed the advantages and challenges of combined eye-tracking and EEG used for this thesis. It concludes that the challenges, as eye-tracking signal loss in young infants, timing delays of the eye tracker and the EEG system and EEG artefacts due to eye-movements and filtering can be overcome by adjusting the methodology. After these numerous corrections and adjustments, the method is an advantageous tool for studying brain mechanisms of attention shift in verbal and non-verbal populations. The programming and methodology was kept constant for different studies in this thesis and the same responses were extracted to allow replication of the results and comparability of methods between different studies and subject groups.

Chapter 3 Eye tracking in the Fixation Shift Paradigm

3.1 Introduction

3.1.1 Attention in infancy

The aim of this study was to develop an automated approach for investigating attention by combining the FSP with eye-tracking. The Fixation Shift Paradigm (FSP) is a well-established behavioural method to examine attention shifts between stimuli in infants, as reviewed in Chapter 1, section 1.3 (review: Atkinson & Braddick, 2012; FPS, e.g. Atkinson et al., 1988; Atkinson et al., 1992; Farroni et al., 1999; Hood & Atkinson, 1993). Chapter 1 (section 1.3) summarised that saccade latencies are longer and numbers of sticky fixations higher when disengagement is required, particularly under 4 months of age (Colombo, 2001; Hood & Atkinson, 1993; Hood et al., 1998; M. H. Johnson et al., 1991). Furthermore, saccades become more accurate with age, reaching the target stimulus more reliably (Aslin & Salapatek, 1975).

As discussed in Chapter 2, previous methods to determine saccadic latencies include observation (e.g Atkinson et al., 1992; Richards, 2005) and video-coding (e.g. Butcher et al., 2000; Elsabbagh et al., 2013; Hood & Atkinson, 1993; Hunnius & Geuze, 2004; Hunnius et al., 2008; Matsuzawa & Shimojo, 1997), which have several disadvantages, including limited spatial and temporal resolution and a lack of automaticity and the opportunity to access that data during testing (Chapter 2, Table 2.1). The current study aimed at combining the FSP with eye tracking to overcome these limitations and to increase accuracy and decrease testing time when investigating attention development, improving the efficiency of using the FSP as an early diagnostic tool and a surrogate outcome measure.

3.1.2 Aims and hypotheses

Eye tracking was used to test infants between 1 and 8 months of age under competition and non-competition conditions. This method was predicted to replicate former findings (Atkinson et al., 1992; Hood & Atkinson, 1993) confirming the latency of the first saccade towards the target to be longer in the competition condition than in the non-competition condition and decreasing with age. Sticky fixations were also expected to be more frequent in competition conditions and decreasing with age.

Furthermore, an increase in trial number in comparison to previous studies was expected, which will allow an analysis of performance over time. Finally, the increased spatial accuracy of the eye-tracker in comparison to former methods will allow an investigation of differences in fixation position in relation to the target. In line with Aslin and Salapatek (1975) it was predicted that young infants' initial saccade will undershoot the target and that infants will then make corrective saccades to fixate it.

3.2 Methods

3.2.1 Participants

Twenty-three infants between 1.42 and 6.73 months of age (M_{age} = 4.19, *SD* = 1.74, 16 female, 7 male) were recruited over the volunteer data base of the Visual Development Unit of University College London. All were born within two weeks of full term and had no record of complications at birth. Parents received reimbursement for their travel expenses. The study was approved by the UCL research ethics committee (Ref. number: 2002/02).

3.2.2 Materials and Stimuli

Each trial started with the first stimulus, a black scheme of a face that changed "expression" at a rate of 3 reversals per second, being presented in the centre of the screen. It subtended a visual angle of 7.7° x 7.7°. The central stimulus remained visible for at least 2 seconds before the target occurred, to avoid the infants getting upset because the stimulus would disappear as soon as they looked at it. When the infant fixated on the face, the second stimulus (target) appeared, a grating made of one black and one white rectangle that reversed colour at a rate of 3 Hz and appeared in the left or right visual field at an eccentricity of 12.9°, subtending a visual angle of 3.1° x 13.2°. In the non-competition condition, the central face disappeared when the peripheral target appeared, while in the competition condition it remained present throughout the trial (*Figure 3.1*).

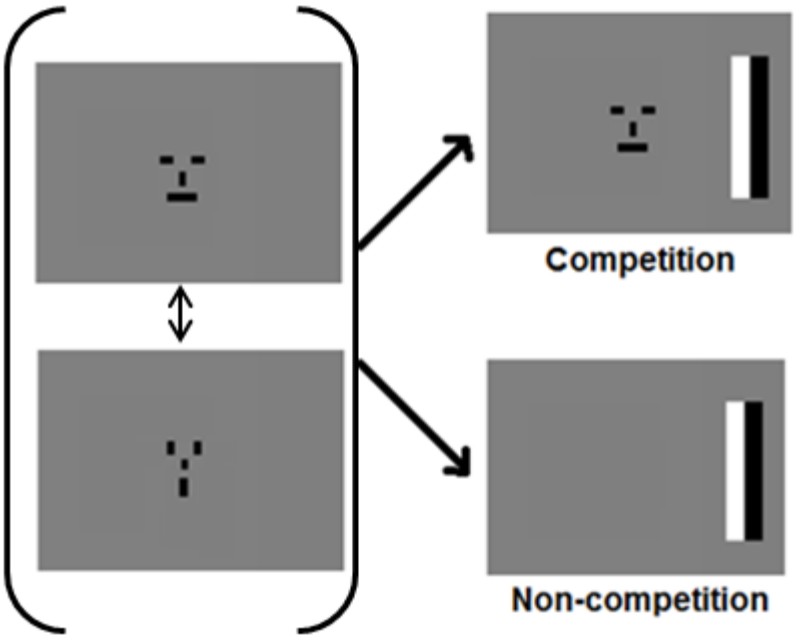


Figure 3.1. Order of displays shown in competition and non-competition conditions. The schematic face changes "expression" at a rate of 3 Hz (see visualisation on the left) and the bars reverse colours to attract the infant's attention.

3.2.3 Procedure

The infant was seated on the parents, caregivers or a researchers lap. The eye-tracker was calibrated on an adult before the experiment started, using a five point routine (see Chapter 2, section 2.2.2 for details). Conditions were presented in a random order. Cartoons were shown between trials to sustain the infants' attention and if the infants showed first signs of boredom, they were turned away from the screen for a few minutes until they appeared attentive again. The experiment continued until the infant got tired or bored, which was usually the case after approximately 10 - 20 minutes.

3.2.4 Design

A mixed design measured the effect of the within-subject factor condition (competition or non-competition) and the between-subject factor age group (younger than 4 months or older than 4 months) on the ability to shift attention, operationalized as the latency of an eye-movement towards the target, on the proportion of trial outcome types (sticky fixations, misdirected saccades) and on the fixation position after a saccade towards the stimulus.

3.3 Results

3.3.1 Data analysis

For the purpose of developmental analysis, infants were separated into two different age groups: younger than 4 months old (n = 11, M_{age} = 2.60, SD = 0.61, range = 1.42 to 3.66 months, 8 female, 3 male) and older than 4 months (n = 12, M_{age} = 5.65, SD = 0.95, range = 4.15 to 6.73 months, 8 female, 4 male), as the main changes in attention shifts have been described to take place between 3 and 4 months (review: Atkinson & Braddick, 2011). The processing and analysis of eye-tracking data is described in detail in the methodology chapter (Chapter 2, section 2.2.4). The gaze position (in degree of visual angle from the centre of the screen) after the first saccade was calculated by averaging across trials after the first saccade towards the correct direction either until the next saccade occurred away from the fixation position or for a maximum of 10 samples. In the following, saccade latencies are displayed in seconds.

3.3.2 Classification of responses

Infants completed an average of 53.26 trials (SD = 20.45, min = 24, max = 86). Less than 12% of trials had to be excluded because of noise, including trials with the fixation not detected on the screen at trial onset (5%), too many large changes in the recorded fixation position, indicating noisy data (<1%), and saccades occurring earlier than 100 ms after target onset (6%). Additionally, some trials showed an initial fixation shift towards the wrong direction (9%). Sticky fixations rarely occurred (<2% of trials).

3.3.3 Latency of re-fixation

The younger group of infants (< 4 months) was slower at shifting attention in the competition condition than in the non-competition condition, as were older infants (*Figure 3.2*). A mixed linear model showed a significant main effect of age, $F(1, 904) = 18.13$, $p < .001$, $d = 0.225$, with longer latencies in the young (M = 0.857, SD = 0.795) than in the old group (M = 0.677, SD = 0.805) and a significant effect of condition, $F(1, 904) = 73.76$, $p < .001$, $d = 0.530$, with shorter latencies in the non-competition (M = 0.563, SD = 0.501) than in the competition condition (M = 0.982, SD = 1.000). There was a significant interaction of age and condition, $F(1, 904) = 8.44$, $p = .004$, with decreasing latencies in the competition condition with age, *Figure 3.2*.

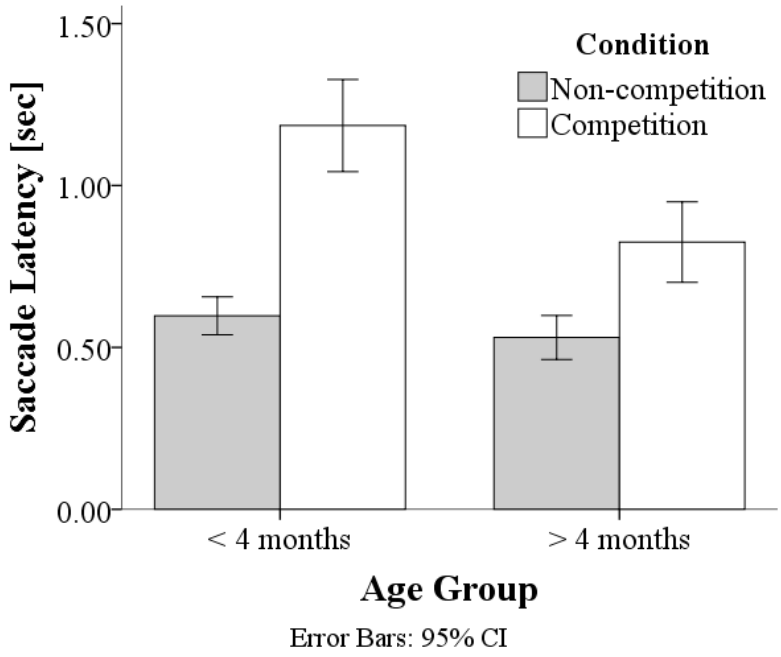


Figure 3.2. Mean time until first saccade for conditions (non-competition and competition) and age groups (younger than 4 months and older 4 months).

3.3.4 Sticky fixations

The proportion of sticky fixations (no saccadic shift within 5 sec after target onset, see Chapter 2, section 2.2.4) was smaller in the non-competition condition than in the competition condition (*Figure 3.3*). A mixed logistic regression showed a significant effect of condition, $z = 5.45$, $p < .001$, and a marginal interaction of condition and age group, $z = -1.91$, $p = .055$, showing a decrease in sticky fixations under competition with age. There were no significant effects of age group or target side.

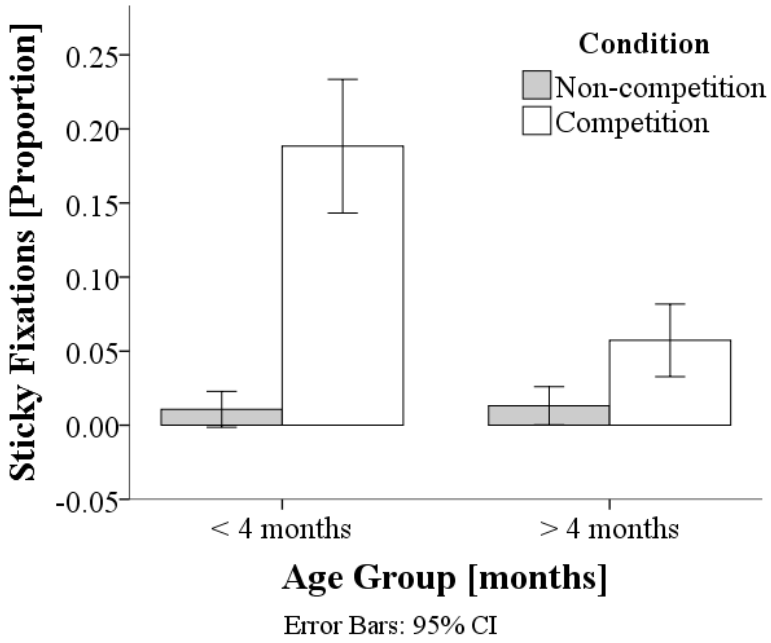
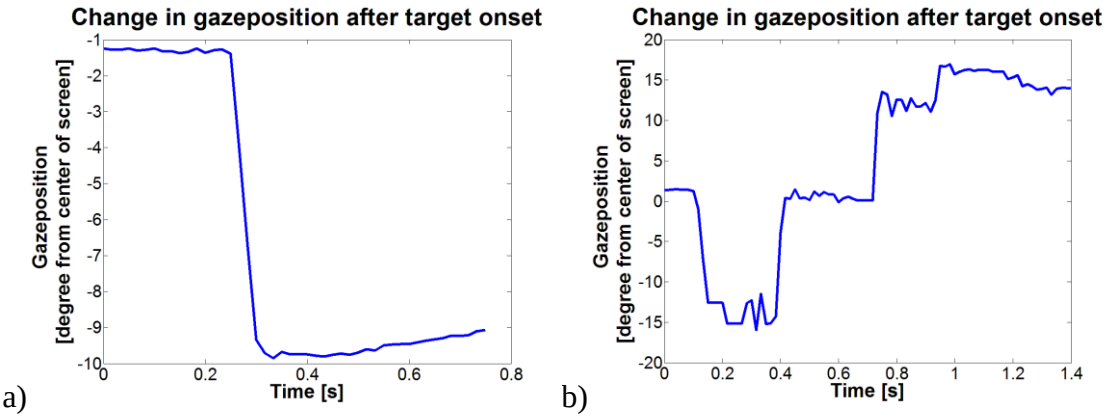


Figure 3.3. Proportion of fixations stuck on the central stimulus in non-competition and competition conditions, separately for infants younger than four months and infants older than four months.

3.3.5 Misdirected saccades

In most trials clear changes in gaze position (saccades) towards one side of the screen could be observed over time (cf. *Figure 3.4*a). However, in 9% of trials the initial saccade was directed to the wrong direction, in 69% of which, the shift towards the wrong direction was quickly followed by one or more corrective saccades towards the target (cf. *Figure 3.4*b).

A mixed logistic regression showed a significant effect of condition on misdirected saccades, $z = 2.99$, $p = .003$, with less misdirected saccades in the non-competition (11%) than in the competition condition (13%). Effects of age or target side were not significant. There were no significant effects on the proportion of saccades that were subsequently corrected.



a) b)

Figure 3.4. Sample data visualising the change in gaze position (0 = centre of the screen) over time after target onset for a trial with a correct re-fixation (left), and a trial with initial saccade towards the wrong direction that is subsequently corrected (right).

3.3.6 Time until saccade to wrong direction

A general linear model for repeated measures showed a significant main effect of condition on latency of saccades to the wrong direction, $F(1, 122) = 4.42$, $p = .038$, $d = 0.504$, and a marginal interaction between age and condition, $F(1,122) = 3.49$, $p = .064$. Saccade latencies to the wrong direction were shorter in the non-competition condition ($M = 0.896$, $SD = 1.033$) than in the competition condition ($M = 1.549$, $SD = 1.514$), *Figure 3.5*. This pattern is comparable to the effects of condition and age group on latencies of saccades to the correct direction; therefore, to investigate similarity of saccade latencies, another model was tested, including the factor correctness of the saccade (correct or incorrect) to predict saccade latency. Correctness had a significant effect on saccade latencies, $F(1, 1023) = 19.08$, $p < .001$, $d = 0.489$, with shorter latencies in correct ($M = 0.761$, $SD = 0.805$) than in incorrect directions ($M = 1.318$, $SD = 1.395$) and there was a significant three-way interaction of condition, age group and correctness, $F(1, 1017) = 4.49$, $p = .034$, suggesting that the decrease of latencies in competition conditions with age was greater for correct than for incorrect saccades.

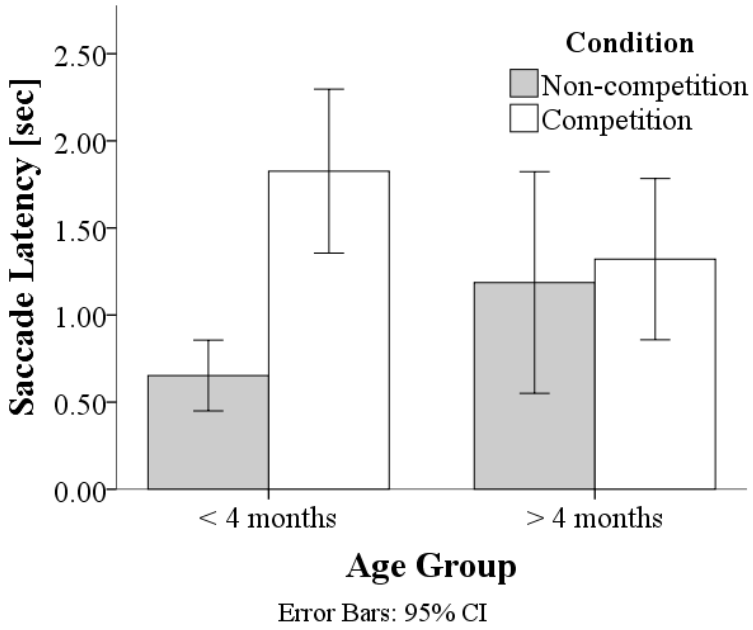


Figure 3.5. Mean latencies of initial saccades to the wrong direction. Saccades of younger infants are slower than of older infants and saccade latencies are generally shorter in the non-competition than in the competition condition.

3.3.7 Gaze position

Younger infants' distance of fixation position from the centre of the screen, i.e. the proximity of their fixation to the target position was smaller than older infants' (*Figure 3.6*). A mixed linear model confirmed a significant difference in fixation position between age groups, $F(1, 21) = 4.73$, $p = .041$, whereas condition did not significantly affect fixation position, $F(1,21) = 0.63$, $p = .438$, nor interact with age group, $F(1,21) = 0.44$, $p = .517$.

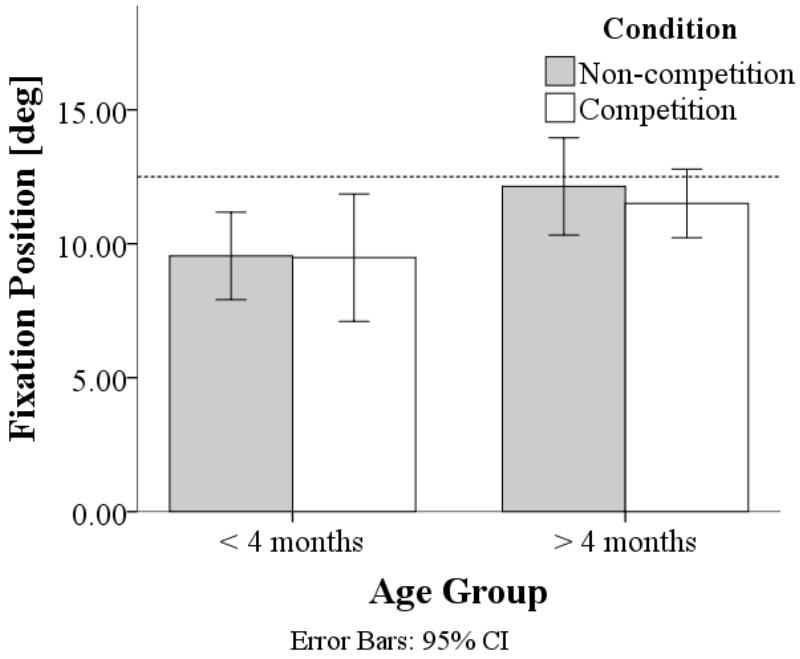


Figure 3.6. Average fixation position from the centre of the screen in degree of visual angle. The dashed line signifies the centre of the target position. Younger infants' fixation position is closer to the centre of the screen than the older infants' in both conditions.

3.4 Discussion

Saccade latencies were higher in the competition condition than in the non-competition condition and higher in the younger group of infants. This is in line with the hypothesis and replicates the findings of former studies (Atkinson et al., 1992; Hood & Atkinson, 1993). Sticky fixations mostly occurred in younger infants under competition. Some saccades were initially directed towards the wrong direction but the majority of them were subsequently corrected. Furthermore, younger infants initially fixated closer to the centre of the screen than older infants, undershooting the position of the target, in agreement with Aslin and Salapatek (1975).

3.4.1 Classification of responses

Infants completed a number of trials (53.26 trials, *SD* = 20.45, *min* = 24, *max* = 86) that is comparable to former studies or exceeds their trial number (20 trials: Atkinson et al., 1992; 27 to 37 trials: Hood & Atkinson, 1993), even when accounting for the number of noisy trials. This supports the prediction that eye-tracking can increase trial numbers. The data loss due to noise was small (<12% of trials) and mostly

caused by trials in which the fixation was not on the centre of the screen at trial onset (5%) or too early to be related to the target (6%). Both of these instances may indicate that the infant was moving or looking around the screen and are therefore probably related to behaviour or inattention of the infant. Less than 1% of trials were lost as a result of excessive noise in the eye-tracking data. *Overall, the data quality indicates that, in the age group tested in this study, eye-tracking can be used to investigate visual attention with a success rate at least as good as previous testing methods.*

3.4.2 Latency of re-fixation

Infants shifted their fixation slower in the competition than in the non-competition condition and they were slower under 4 months of age than over 4 months. Those findings confirm the prediction that infants have difficulties disengaging their attention under competition, whereas they are quicker at shifting attention to a new target when the competing stimulus disappears. The ability to disengage improves with age as indicated by the interaction effect of age and condition. These results are in line with adult observer findings using the Fixation Shift Paradigm (Atkinson et al., 1992; Hood & Atkinson, 1993). Given that the FSP can be used as a predictor of developmental delays and a diagnostic tool to identify high-risk groups for attention difficulties (review: Atkinson & Braddick, 2012; Atkinson et al., 2003; Atkinson et al., 2008; Braddick et al., 1992), eye-tracking should improve its usability, as it avoids the need for experienced adult observers, and provides more trials in a shorter testing time, both of which are likely to be important in a clinical context.

And finally, the eye-tracking data can be analysed by the computer immediately while the experiment is still running. This allows for eye-tracking data to be processed and fed back into the stimulus presentation programme, allowing to combine the behavioural measures with other methods that need high temporal accuracy, for example electroencephalography (EEG). Although the results support the idea that the developmental improvement in competition performance requires cortical control of the reflex-like subcortical attention (cf. Atkinson, 1984, 2000a; Atkinson & Braddick, 2012; Atkinson & Hood, 1997; Atkinson et al., 1992; Braddick & Atkinson, 1988; Braddick et al., 1992; Hood, 1995; Hood & Atkinson, 1993; Hood et al., 1998), behavioural measures can only prompt speculations about underlying brain mechanisms without directly measuring brain responses. The possibility to combine the FSP with EEG owing to the better timing achieved by eye-tracking allows to gather neural data.

Studying the time-course of target-induced brain responses in different areas of the brain will give an insight into how the cortical control of attention develops. Combining behavioural and neural measures can therefore help uncover the functional brain mechanisms involved in attention development to complement the current knowledge about structural development (Huttenlocher, 1979; Petanjek et al., 2011).

3.4.3 Sticky fixations

"Sticky fixations" only rarely occurred, confirming that the latency of re-fixations should not be distorted by data in which infants failed to shift within the defined time after target onset. The low number of sticky fixations showed a pattern in line with former studies indicating that infants rarely fail to shift gaze after an age of two months (Atkinson et al., 1992; Hood et al., 1998; M. H. Johnson et al., 1991). In the current paradigm, target bars were slightly closer to the centre of the screen than in former studies (Hood & Atkinson, 1993), as reviewed in Chapter 2, section 2.2.1, making it easier for infants to detect and shift towards them. However, sticky fixations occurred more often in the competition condition and in younger infants, an effect that is comparable to results of former studies (Atkinson et al., 1992; Hood et al., 1998; M. H. Johnson et al., 1991).

3.4.4 Misdirected saccades

Eye-tracking was confirmed to give a detailed insight to the time course of gaze positions, permitting an investigation of the phenomenon of saccades towards the wrong direction. Those fixations were not preferably directed to one screen side, indicating that they were not caused by specific features of the set up or the position of the researcher, who was mostly standing on the same side of the room. The majority of misdirected saccades were subsequently corrected, indicating that they did not reflect a complete failure to detect the target. In some cases the saccades might have been caused by a loss of interest leading to the infant looking away. Another reason for misdirected saccades could be a faulty execution of the target response. Infants might expect a target to appear as soon as they perceive the central face stimulus. This expectation would then lead to a prediction of the screen side on which the target would appear resulting in a premature reaction that can be wrong in half of the cases. In a less conscious way, the infant's brain might learn to execute a cognitive and behavioural programme for shifting

gaze in response to the target. This programme might be applied in a faulty way resulting in it being executed to the wrong direction.

3.4.5 Timing of wrong saccades

Infants show longer saccade latencies in the competition condition than in the non-competition condition irrespective of whether they shift towards the correct or the incorrect screen side. This supports the current expectation that infants have difficulties disengaging from a foveated stimulus no matter where there saccade is directed to. Furthermore it indicates that the longer saccade latencies under competition cannot be attributed to infants processing the peripheral stimulus less, as they also take longer to disengage to a direction where there is no stimulus. Effects from saccades to the wrong direction provide further support that disengagement is the crucial process that determines the ability to shift gaze under competition.

3.4.6 Gaze position

Results suggest that younger infants initially fixate closer to the centre of the screen and therefore further away from the target, which supports the assumption that young infants tend to initially undershoot the target as suggested by Aslin and Salapatek (1975). Aslin and Salapatek (1975) suggest that saccades might get programmed for the distance to the target, but the execution of the saccade is faulty leading to an undershooting of the target. As competition and non-competition conditions of the FSP did not affect the scope of the initial saccade, disengagement of attention does not seem to be responsible for difficulties in fixating on the target position. Our results therefore give room for the possibility that execution or motor control of eye-movements is not properly functional in younger infants, whereas no support for an effect of attention programmes on saccade end position could be found.

3.4.7 Methodology

The eye-tracker was calibrated on an adult before testing instead of calibrating each infant individually because the inexact calibrations that are achieved when running a calibration routine on infant subjects often lead to missing data and bad accuracy. As the eye-tracker has been calibrated on a person with different pupil and head size, its spatial accuracy is not ideal. Given that only relative and not absolute positions were investigated, the ratio can still give insights to approximate fixation positions. However,

the calibration on adult observers who would on average have a bigger head size than infants might lead to distortions of fixation position that affects younger infants more than older infants as their head size is on average smaller. This might account for the fixation position differences found between younger and older infants. To exclude this possibility, adults were tested in the same paradigm and their fixation positions were compared to infants (Appendix E). Results suggest that despite the difference in head circumference in the older infant group (> 4 months) and adults, there were no significant differences in fixation position between both groups, suggesting that head size or properties cannot account for the findings of young infants undershooting targets.

Despite the debatable spatial accuracy, eye-tracking provides good temporal resolution. The temporal accuracy required to determine saccade latencies should be unaffected by slight distortions of spatial accuracy. The sampling rate of 60 Hz in this study allows measurement of the saccade latencies to within 16.7 ms, as well as a detailed inspection of different steps during the disengagement process. *In general, eye-tracking can increase accuracy and lead to higher trial numbers, suggesting that this methodology outmatches previous methods for studying attention and permits the detection of further behavioural phenomena in attention tasks.*

3.4.8 Summary and conclusion

On the whole the results confirm that eye-tracking can be used to automate the Fixation Shift Paradigm and that it leads to a comparable, if not higher trial number, allowing for shorter testing times and an efficient use of the FSP as an early diagnostic tool. Findings of former studies were replicated, confirming the importance of the ability to disengage for attention development. Eye-tracking gives more detailed insights to the correction of saccades, prompting speculations about malfunctions in pre-programmed reaction processes. The monitoring of gaze position confirms an initial undershoot of the target in younger infants, suggesting an increase in saccade accuracy between 1 and 8 months. In conclusion, eye-tracking can efficiently give precise insights to attention development. *This experiment in this chapter confirms that it is possible to combine the FSP with eye-tracking in non-verbal populations, providing the basis of an automated approach that can be combined with EEG.* The following chapters will combine eye-tracking with EEG to simultaneously measure saccadic shifts and their coinciding neural responses.

Chapter 4 Comparison of EEG responses associated with covert and overt attention shifts in adults

4.1 Introduction

The previous chapter showed that it is possible to combine the FSP with eye-tracking to collect saccadic shift data with a fairly high temporal accuracy of 60 Hz, which furthermore allows evaluation of the data in real-time, making it possible to use this data as automatic input for controlling the experimental sequence and as triggers for EEG analysis of brain responses. This chapter reports an experimental design combining eye-tracking data and EEG to simultaneously monitor eye movements and brain responses. This method of investigating brain mechanisms of attention shifts has several advantages, which will be discussed below, including its usability for non-verbal and infant subject groups. However, most previous research has investigated brain mechanisms of covert attention shifts, to ensure cleaner EEG data. One aim of this chapter was therefore to create a bridge between previous studies on covert attention shifts and the FSP shifts involving eye-movements by letting subjects perform an identical task in which they either shifted their attention overtly making a saccadic shift as a response, or covertly by attending and manually responding to the peripheral visual stimulus when it appeared but maintaining fixation in the centre.

4.1.1 Combining eye-tracking measures and EEG

The previous chapters showed that non-verbal tools, like the FSP, often rely on natural eye-movements to indicate where visual attention was overtly shifted (Atkinson & Braddick, 2012; Atkinson et al., 1988; Atkinson et al., 1992; Farroni et al., 1999; Hood & Atkinson, 1993; Hood et al., 1998; Matsuzawa & Shimojo, 1997). It was furthermore established that some neurodevelopmental disorders coincide with language impairments (Chapter 1, section 1.3.2), making it desirable to develop a measure of attentional brain mechanisms that can be adjusted to be used non-verbally.

Chapter 2 reviewed the evidence that the combination of eye-movement based measures with EEG is intricate as eye movements can lead to artefacts, distorting the potentials recorded from the scalp (Corby & Kopell, 1972; Croft & Barry, 2000; Joyce et al., 2004). Therefore, brain correlates of attention have mostly been studied using tasks in which participants were explicitly instructed to keep their gaze fixed to avoid artefacts in the ERP data and make manual responses to targets (e.g. Di Russo et al.,

2001; Heinze et al., 1994; Kim et al., 2007; M. M. Müller, 1998; M. M. Müller & Hillyard, 2000; Posner et al., 1984). Our preliminary findings (Kulke & Wattam-Bell, 2013; Kulke, Wattam-Bell, Atkinson, & Braddick, 2014b) suggest that it is possible to measure ERPs in tasks similar to the FSP, if the analyses concentrate on potentials that are measured before the saccade onset (Luck, 2005) or occur in more posterior areas of the brain (Lins, Picton, Berg, & Scherg, 1993).

The aim of this chapter was therefore to combine eye tracking and EEG to measure overt attention shifts and to compare the results to previous results on covert attention shifts.

4.1.2 Brain responses during covert attention shifts

Neural responses commonly found for visual stimuli are reviewed in Chapter 2, section 2.3.2, and are predicted to also occur in this study of visual attention. The review of attentional modulations of brain responses (Chapter 2, section 2.3.2) suggests that the following attention responses may be observed during attention shifts

1. A posterior visual response (P1-N1 complex) that shows enhanced amplitudes for attended targets (e.g. Harter et al., 1982; Heinze et al., 1990; Luck et al., 1990; Mangun, 1995; Rugg et al., 1987), peaks in the contralateral before the ipsilateral hemisphere (Rugg et al., 1987) and decreases with increasing numbers of stimuli in the visual field.
2. A frontal negativity that is affected by covert visual spatial attention (e.g. Harter et al., 1982; Heinze et al., 1990; Rugg et al., 1987).
3. Early frontal responses related to saccade preparation, which have previously been reported in in-brain recordings in epilepsy patients (Kirchner et al., 2009).

Most covert attention shift tasks involved discrimination of a target feature which is specified top-down, for example depending on target colour (Harter et al., 1982), target size (Mangun, 1995), flash duration (Rugg et al., 1987) or features of letters (Heinze et al., 1990; Luck et al., 1990), making the tasks more complex than a simple attention shift. Their tasks therefore both involve a top-down attention component that requires verbal instructions and the bottom-up response to the target and it is unclear which of these responses lead to the observed neural response patterns. In

contrast, the current study purposefully kept the response simple to ensure that infants and populations with developmental disorders should be able to complete the same task without verbal instructions, as demonstrated in Chapter 3.

4.1.3 Difference between saccadic and motor responses

The current chapter describes results from comparing ERPs preceding saccadic or motor responses, examining how the response type itself may affect findings. Differences between overt and covert attention shift tasks can occur on several levels, either caused by the explicit instruction of subjects to inhibit their natural eye-movements or by the different response type (manual response or saccade). It is therefore important to consider the effect of these factors. On a behavioural level, manual responses differ from saccadic responses, showing slower response latencies (e.g. Bekkering, Adam, Kingma, Huson, & Whiting, 1994; Bekkering, Pratt, & Abrams, 1996; Briand, Larrison, & Sereno, 2000). Differences can also appear on a neural level. Reflex-like directing of attention naturally takes places without subjects being explicitly instructed (bottom up attention). If, however, subjects are instructed to keep their gaze still, this can lead to effects on behaviour and brain responses. Previous literature shows that the PFC and FEF are involved in suppressing unwanted reflexive eye-movements (Miller, 2000; Rafal et al., 2000). Potentials in these areas may depend on the effect of these instructions instead of the actual attention shifting process, leading to different patterns of brain activation in explicitly instructed and natural tasks. It is unclear to what extent the eye-movement suppression leads to different brain responses in the FSP. Therefore, this study aimed to investigate differences in patterns of behaviour and brain responses by directly comparing a task in which the gaze is moved towards the target with a task in which participants were instructed to keep their fixation still.

Different brain responses can be found prior to eye-movements and motoric responses (Moster & Philadethia, 1991). *Premotor potentials* include a readiness potential (“Bereitschaftspotential”) which is a negativity occurring in central regions, more pronounced on the contralateral hemisphere, 500 ms before a movement. It is under debate whether this potential is equivalent to the contingent negative variation (CNV), which can also be found without motor responses (Caldara et al., 2004). It is followed by a premotor positivity that occurs in bilateral parietal regions. Most motor-related potentials occur later than 180 ms after target offset, which was the interval

investigated in this study, and are therefore unlikely to be present in the time window extracted here.

Saccades that are voluntarily conducted in darkness are preceded by an early pre-saccadic negativity (PSN) appearing in posterior frontal or vertex regions, 650-800 ms before saccade onset; however, this response does not occur for visually-triggered saccades (Moster & Philadethia, 1991). It is followed by the pre-saccadic positivity (PSP) appearing in bilateral parietal areas 32-250 ms before saccade onset. Directly before saccade onset (0-40 ms), the spike potential, a sharp negativity appears in anterior regions. It is unclear whether it reflects ocular motor responses or muscle activity. Pre-saccadic potentials have been linked to frontal regions of the brain, specifically the FEF (Moster & Philadethia, 1991). They have been commonly analysed by extracting the EEG data preceding the saccade (e.g. Csibra et al., 1997; Csibra et al., 1998; Moster & Philadethia, 1991). If an ERP is locked to the response, extracting stimulus-locked ERPs can cause "latency jitter" in the analysis (Caldara et al., 2004). The aim of this thesis was to identify changes in the ability to shift attention that are likely to be related to a disengagement from competing stimuli and triggered by the onset of a new stimulus. It is plausible, that the disengagement is at least partially related to the stimulus onset. Therefore, EEG data was extracted following the stimulus onset instead of preceding the saccade, allowing a stimulus-locked ERP analysis. Differences in fronto-central responses between overt and covert attention shifts related to saccade planning may be visible in this study, as these responses lie between stimulus appearance and saccade execution and therefore might be partially stimulus-locked. However, it is also possible that these responses occur closer towards the saccade and therefore fall outside the extracted time window.

4.1.4 Extraction of attention responses

Visual responses to stimuli can overlap with attentional responses, making it difficult to discriminate between them (e.g. Heinze et al., 1990; Luck et al., 1990). As the standard FSP (Chapter 3) requires subjects to direct attention to a visual target on *one* side of the screen, the lateralised attention and lateralised visual responses to this stimulus might overlap. Therefore, an additional condition was introduced in the experiment described in this chapter, in which identical stimuli were presented in *both* visual fields, leading to identical visual input, meaning that lateralised visual responses would occur in both hemi fields. However, subjects could only direct their attention to

one of the stimuli, meaning that the lateralised attention response should only appear related to either the left or the right field. Attention responses should be more distinguishable from visual responses in this condition. However, as several stimuli are visible, the general responses may change, as the number of stimuli can influence response magnitude, decreasing with number of stimuli (Keitel et al., 2013; Luck et al., 1997; Moran & Desimone, 1985), while attention effects become larger the more stimuli are visible (Luck et al., 1997).

4.1.5 Research question and hypotheses

The experiment described in this chapter aimed to compare the brain responses in overt and covert attention shift tasks to allow a comparison of previously used instruction-based tasks and the FSP for non-verbal populations. Behaviourally, manual responses were expected to show longer latencies than saccades (Bekkering et al., 1994; Bekkering et al., 1996; Briand et al., 2000) and responses to single targets were expected to be faster than to double targets. Similar visual responses should occur in covert and overt attention shift tasks, including a posterior positive ERP response. In line with previous research the magnitude of these responses should decrease with target number. Fronto-central areas should be involved in attention shifts and more strongly related to saccades than to shifts involving manual responses, while covert shifts may show frontal inhibitory activation related to the inhibition of eye movements.

4.2 Method

4.2.1 Participants

Twenty-four students (20 female) from the UCL Psychology subject pool with a mean age of 21.3 years (*SD* = 2.4, range = 18 to 28 years) participated in the study in return for monetary compensation (£10) or course credit. All had normal or corrected-to-normal vision and no known history of brain disease. Twenty-three were right-handed. One female subject was excluded because of a technical error. The study was approved by the UCL ethics committee (Ref. number: CPB/2013/011 and CPB/2014/007).

4.2.2 Materials and Stimuli

Testing equipment and settings were kept constant as described in the methodology chapter (see Chapter 2, section 2.2.1). In addition to the previously described set up a joypad (Saitek USB V pad) was used to monitor participants' manual responses. At the beginning of each trial, a white dot with a size of 0.7 degree of visual angle appeared in the centre of the screen for a randomised inter-trial interval between 0.5 and 2.5 seconds. When the subject fixated on the dot after the random inter-trial interval, target stimuli randomly appeared on the left, right or on both sides of the screen at an eccentricity of 12.9° of visual angle, while the dot remained present. The target stimuli were the same as in Chapter 3, being phase reversing black and white rectangular bars subtending a visual angle of 3.1° x 13.2°, with a reversal rate of 3 Hz (*Figure 4.1*).

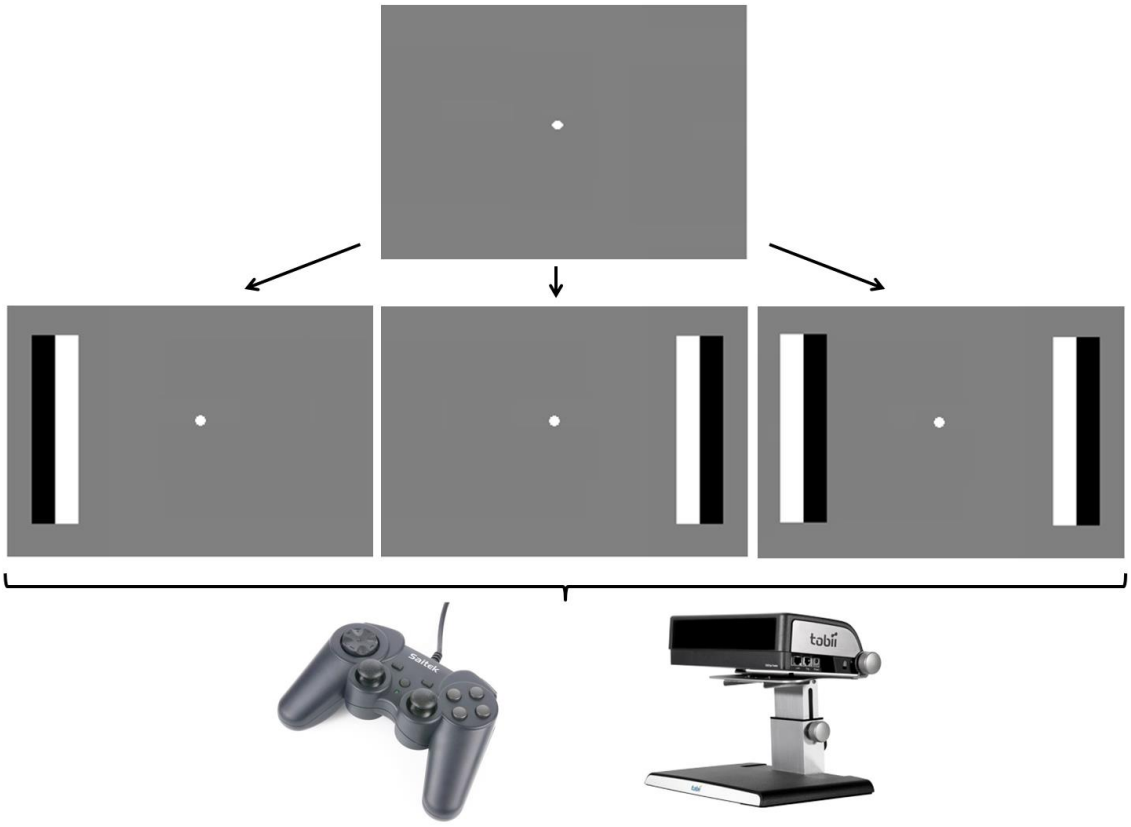


Figure 4.1. Trial timing. A fixation dot appears in the centre of the screen followed by phase reversing bars on the left, right or both sides of the screen. Subjects respond by pressing buttons on a joypad (block 1) or by making eye-movements towards the bars (block 2).

4.2.3 Procedure

EEG was recorded while the subjects were engaged in the behavioural tasks. After the eye-tracking calibration (see Chapter 2, section 2.2.2 for details) the main experiment started. In all conditions, a white fixation dot appeared in the middle of the screen. In the manual response condition, participants were instructed to fixate on this dot while keeping their gaze as still as possible and to press a button that corresponded to the side on which the peripheral targets appeared. When targets appeared on both sides of the screen they were instructed to choose a button to press on either the left or the right. In the eye-tracking conditions, participants were instructed to initially focus on the white central dot and to look at the target as soon as it appeared. When targets appeared on both sides of the screen they were instructed to choose a screen side to make the saccade to the bar.

4.2.4 Design

In a 2x2x2 within subject design the effect of the factors response type (manual or saccadic), number of targets (1 or 2), and screen side responded (left or right) on behavioural response latency was measured. For the extracted neural responses, the effect of response type (manual or saccadic), number of targets (1 or 2), brain hemisphere (ipsilateral or contralateral to the target responded to) and brain side (left or right side of the brain) on ERP latencies and amplitudes were computed. Note that there are two measures for brain lateralisation: *brain hemisphere* describes the lateralisation in relation to the target (hemisphere ipsi- or contralateral to the stimulus that was reacted to) and because neural models of attention suggest a right-lateralised attention network, the factor *brain side* compares the left and right side of the brain. Mixed models were used for multivariate analyses. Manual and saccadic conditions were tested in separate blocks; other variables were randomly varied within these blocks. To avoid undesired eye-movements in the manual conditions, manual conditions were completed first. Both the manual and the eye-tracking conditions consisted of four blocks of 100 trials. Short breaks were given between each set of 100 trials, with longer breaks occurring after 300 and 600 trials while the experimenter readjusted the electrode impedance. The entire experiment lasted for approximately one and a half hours.

4.3 Results

4.3.1 Data Analysis

Detailed data processing procedures were kept constant across all experiments in the thesis, as described in Chapter 2, section 2.2.4. For valid trials the latency of saccades was calculated as the difference in time between target onset and first lateral saccade towards it and latencies were averaged within conditions. In manual trials, mean reaction time was calculated as the time between target onset and button press and averaged within conditions. EEG data was processed as described in Chapter 2, section 2.3.3. The average individually calculated noise threshold for ERP samples (based on the individual subject's MAD threshold) was 13.6 µV (*SD* = 6.80 µV) for saccade trials and 13.6 µV (*SD* = 5.29 µV) for manual response trials, $t(23) = -0.45$, $p = .965$, and the individual range threshold in amplitude was on average 53.9 µV (*SD* = 26.2 µV) for saccades and 53.1 µV (*SD* = 18.5 µV) for manual responses, $t(23) = 0.15$, $p = .881$. The mean number of trials subjects successfully completed behaviourally was 395 (*SD* = 9.83) trials per subject for saccades and 387 (*SD* = 24.7) for manual responses, $t(23) = 1.67$, $p = .109$. After exclusion of noisy EEG data, an average of 368 (*SD* = 15.8) saccade trials and 357 (*SD* = 29.0) manual response trials per subject remained in the analysis, $t(23) = 2.11$, $p = .046$.

4.3.2 Behavioural results

A mixed-effects linear model with participants as a random effect was calculated to predict reaction time from the factors screen side that was responded to (left or right), number of targets (one or two) and response type (manual or saccadic response).

Response latencies were significantly shorter in saccadic conditions (*M* = 0.308 sec, *SD* = 0.038) than in manual response conditions (*M* = 0.480 sec, *SD* = 0.098), $F(1, 154) = 521.61$, $p < .001$, $d = 2.317$, and significantly higher to double targets (*M* = 0.406 sec, *SD* = 0.121) than to single targets (*M* = 0.382 sec, *SD* = 0.104), $F(1, 154) = 10.35$, $p = .002$, $d = 0.214$ (*Figure 4.2*). No other main effects or interactions were observed.

In summary, responses were faster towards single than towards double targets and saccades were faster than manual responses.

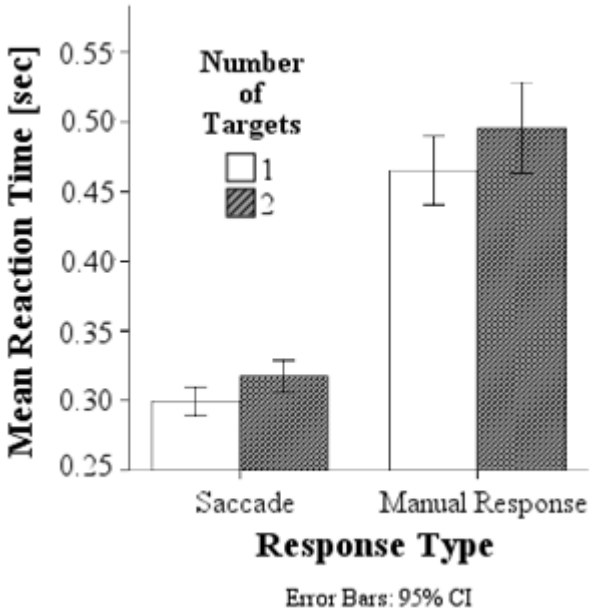


Figure 4.2. Effects of response type and number of targets on response latencies.

4.3.3 EEG Results

The most prominent ERP responses are displayed in the topographical plots in *Figures 4.3 to 4.5*. Detailed topographical plots and wave plots of the brain responses to single and double targets in manual and saccadic response conditions are displayed in Appendix F.1. Amplitudes are plotted on a colour spectrum from red (positive response, 2 µV) to blue (negative response -2 µV), *Figures 4.3-4.5*.

Neural responses include an early posterior positivity that only occurred in saccade conditions (*Figure 4.3*). It was followed by a later positivity in manual and saccade conditions that was more pronounced in the ipsilateral hemisphere to the selected target and more pronounced for single than for double targets (*Figure 4.4*). It coincided with a fronto-central negativity.

In double target conditions, the response was followed by a strong frontal positivity that coincided with a negativity that was slightly more pronounced in the left side of the brain, independent of the target location (*Figure 4.5*).

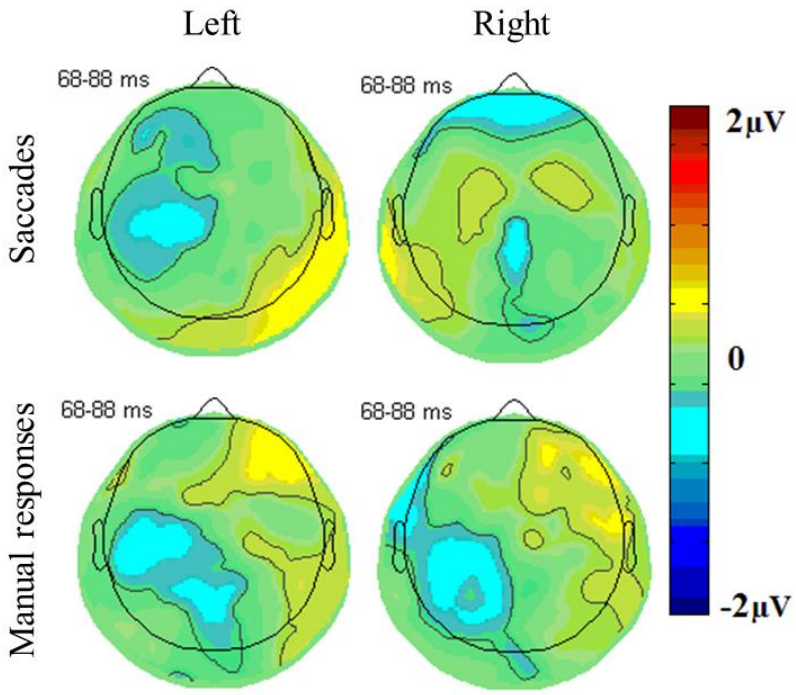


Figure 4.3. Topographical plots of the earliest response. An early contralateral positivity towards single targets on the left (left plots) and right (right plots) screen side is only visible for saccades (top) but not for manual responses (bottom).

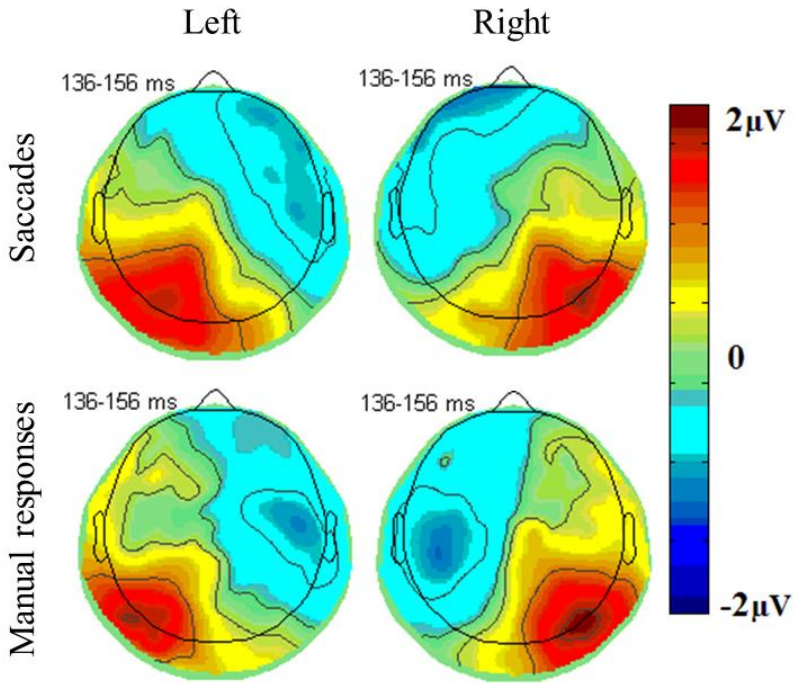


Figure 4.4. Topographical plots of the posterior positivity. A later posterior response to single targets on the left (left plots) and right (right plots) side of the screen is more pronounced in the ipsilateral hemisphere for both saccades (top) and manual responses (bottom) and coincides with a fronto-central negativity.

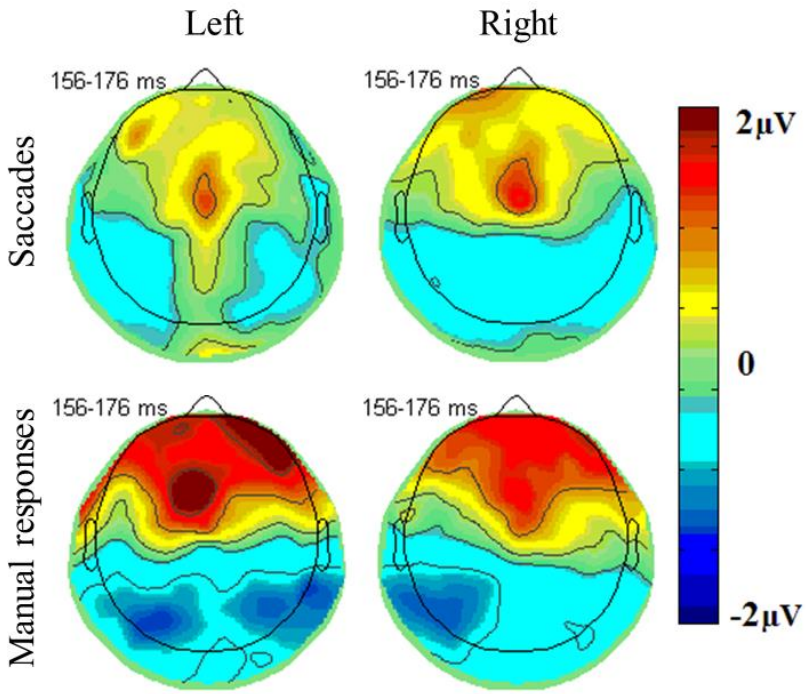


Figure 4.5. Topographical plots of a late response in double target conditions. Double target trials in which subjects subsequently responded to the right (right plots) or left (left plots) target show a late frontal positivity coinciding with a posterior negativity for both saccades (top) and manual responses (bottom) that is not lateralised with respect to the selected target but slightly more pronounced in the left side of the brain.

Topographical difference plots of the difference between saccadic minus manual conditions (Appendix F.2) show that the posterior response is more positive for saccades than for manual responses and lasts longer. The frontal positivity is stronger in manual conditions than in saccadic conditions.

Linear mixed models including participants as random effects were calculated to predict response amplitudes and latencies from the fixed factors response type (saccade or manual response), number of targets (one or two), brain hemisphere (ipsilateral or contralateral to the target) and brain side (left or right). In the following, amplitudes are displayed in µV, ERP latencies are reported in ms.

Posterior responses

Responses were extracted in two electrode clusters around the occipital electrode locations O1 and O2 (see Chapter 2, Figure 2.4 and section 2.3.2 for details on the extracted electrodes). Occipital areas showed a small early positivity, peaking between

40 and 90 ms after target onset that was followed by a greater positivity between 100 and 180 ms (*Figure 4.6* and *Figure 4.7*). They were followed by a negativity that was more pronounced in manual response conditions. As it peaked towards the end or outside the analysed window, the negativity was not analysed further to avoid ceiling effects.

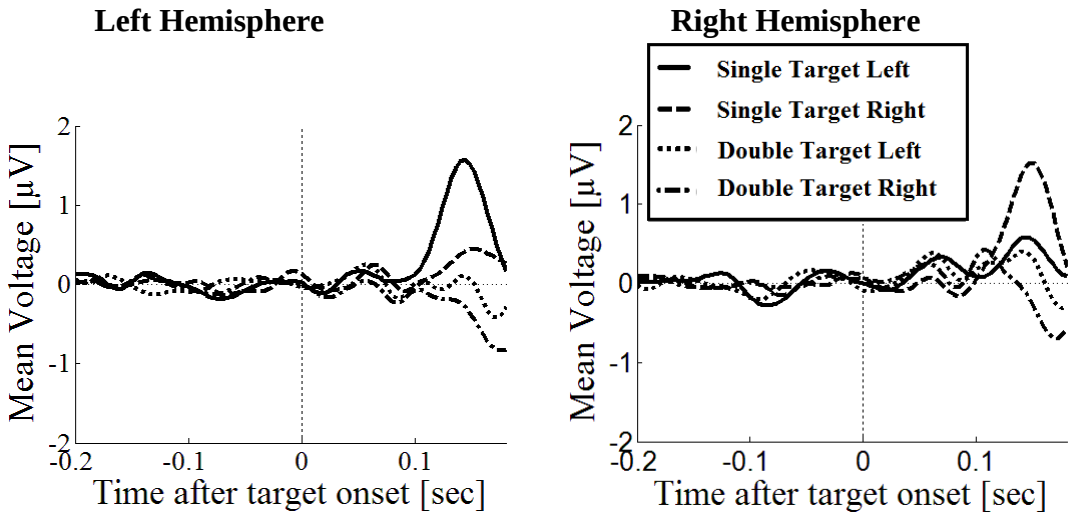


Figure 4.6. Wave plot of the occipital response for *saccade conditions* in the left hemisphere (left) and the right hemisphere (right) of the brain.

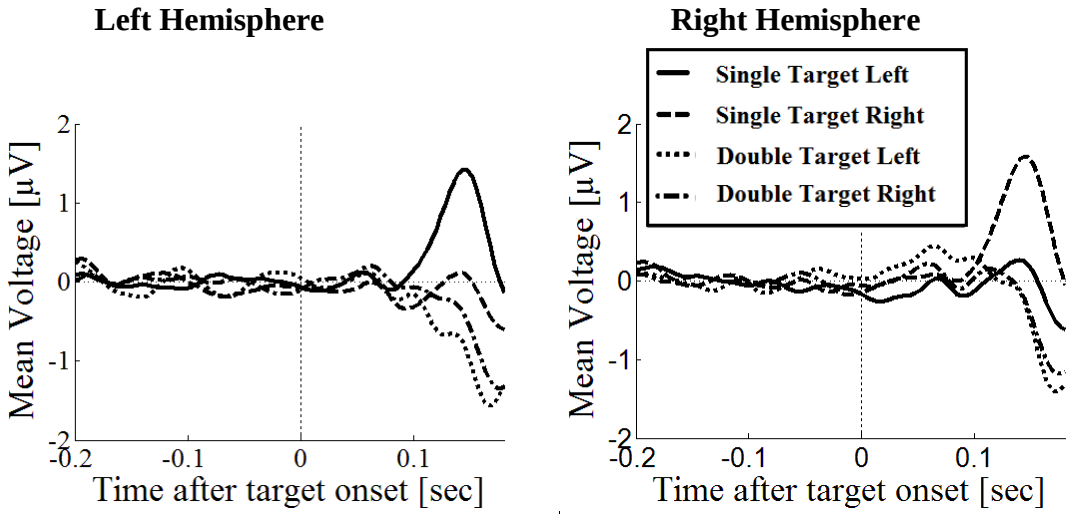


Figure 4.7. Wave plot of the occipital response for *manual response conditions* in the left hemisphere (left) and the right hemisphere (right) of the brain.

Early posterior positivity

The early positivity peaked around 66.5 ms after target onset (*SD* = 19.2) with an average amplitude of 0.65 µV (*SD* = 1.88 µV). Peak amplitude was significantly affected by target number, $F(1, 330) = 5.11$, $p = .024$, $d = 0.219$, with larger amplitudes for single targets (*M* = 0.86, *SD* = 1.79) than for double targets (*M* = 0.45, *SD* = 1.95). There was a marginal three-way interaction of target number, hemisphere and brain side, $F(1, 330) = 3.42$, $p = .065$, *Figure 4.8*. Peak latency showed no significant main or interaction effects.

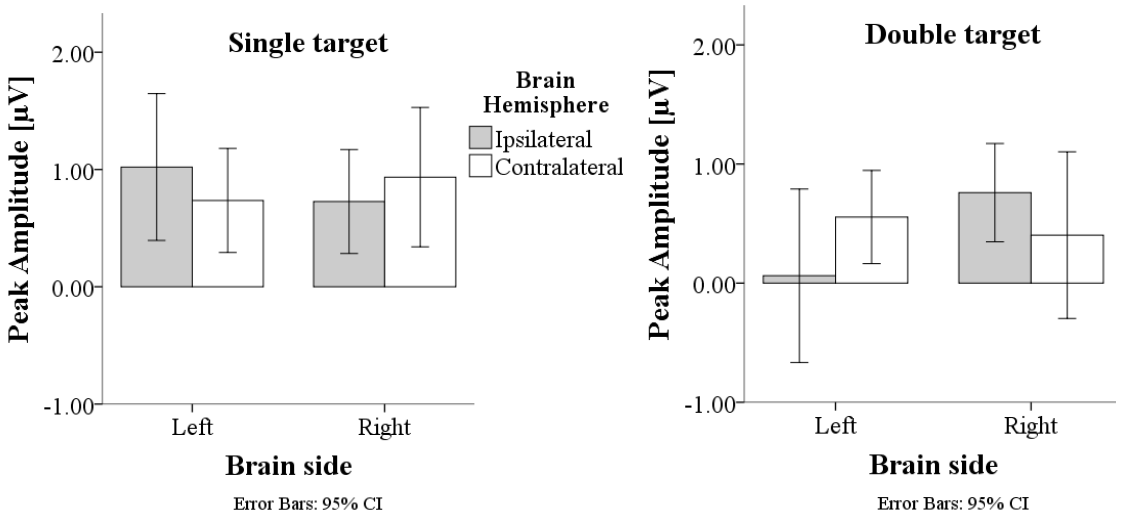


Figure 4.8. Three way interaction of number of targets, brain side and brain hemisphere on peak amplitude of the early posterior positivity.

In summary, the early posterior peak was greater for single than for double targets and showed marginally different lateralisation effects depending on target number.

Later posterior positivity

The later posterior positivity peaked around 141 ms after target onset (*SD* = 26.2) with an average amplitude of 1.42 µV (*SD* = 2.63 µV). Peak amplitude was significantly affected by number of targets, $F(1, 330) = 23.59$, $p < .001$, $d = 0.457$, with higher amplitudes for single (*M* = 2.01, *SD* = 2.54) than for double targets (*M* = 0.83, *SD* = 2.60), and showed a marginal interaction effect of number of targets and hemisphere, $F(1, 330) = 3.19$, $p = .075$, with greater ipsilateral amplitudes for single targets but not for double targets (*Figure 4.9*).

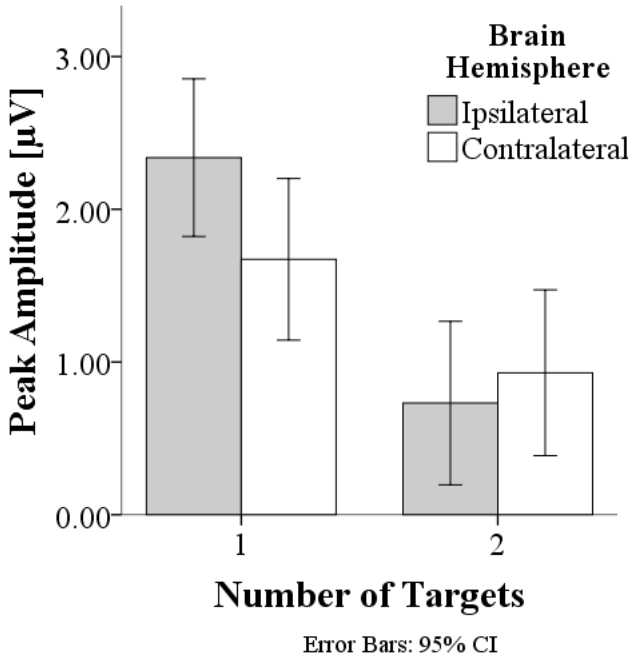


Figure 4.9. Interaction effect of number of targets and hemisphere on occipital peak amplitude. Single targets show greater ipsilateral than contralateral amplitudes, while there is no significant difference between hemispheres for double targets.

Peak latencies showed a significant effect of number of targets, $F(1, 330) = 20.16$, $p < .001$, $d = 0.348$, with significantly longer latencies for single targets ($M = 146$, $SD = 26.1$) than for double targets ($M = 136$, $SD = 29.5$), and an effect of response type, $F(1, 330) = 19.08$, $p < .001$, $d = 0.364$, with significantly longer latencies in saccade conditions ($M = 145$, $SD = 26.1$) than in manual conditions ($M = 136$, $SD = 25.5$).

In summary, the later posterior positivity had greater amplitudes towards single than double targets, especially in the ipsilateral hemisphere. Peak latencies were shorter for double targets and shorter for manual response conditions.

Frontal responses

Frontal responses were extracted in two lateral fronto-central electrode clusters (see Chapter 2, Figure 2.5 and section 2.3.2 for details on the extracted electrodes). Detailed wave plots of different electrode locations are displayed in Appendix F.1. Frontal areas showed a negativity between 100 and 180 ms after target onset that was followed by a positivity, peaking towards the end or outside of the extracted time window (*Figure 4.10* and *Figure 4.11*).

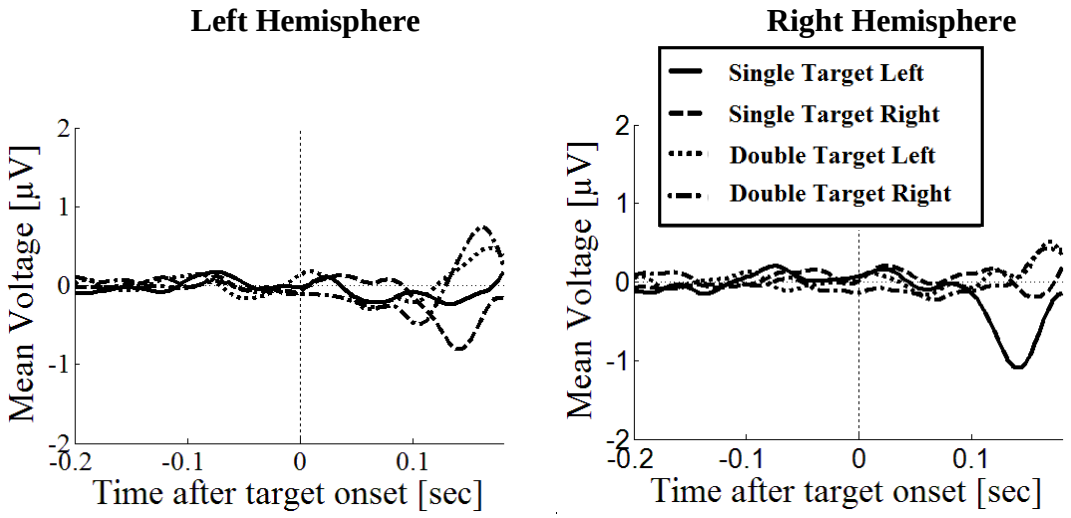


Figure 4.10. Wave plot of the frontal response for *saccade conditions* in the left hemisphere (left) and the right hemisphere (right) of the brain.

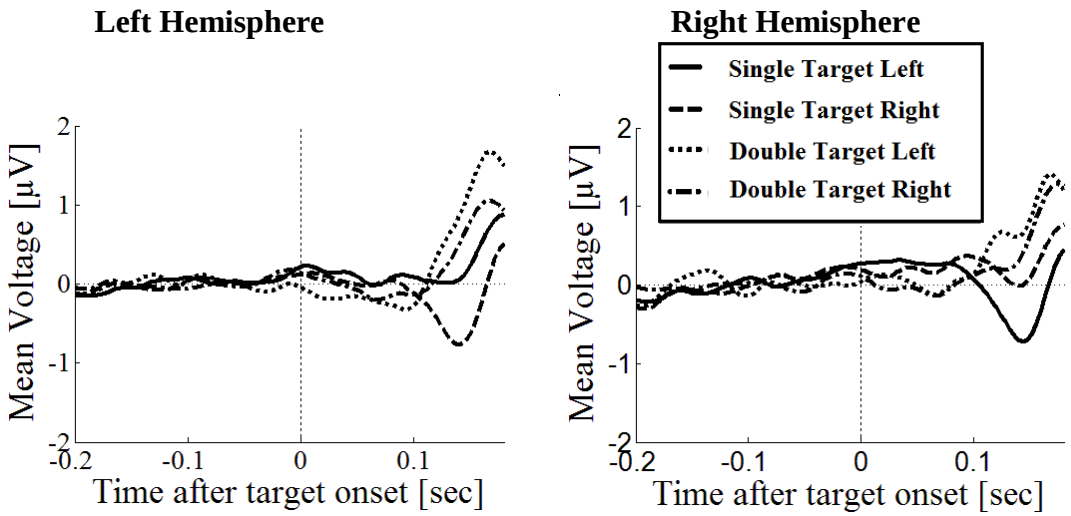


Figure 4.11. Wave plot of the frontal response for *manual response conditions* in the left hemisphere (left) and the right hemisphere (right) of the brain.

Frontal negativity

The frontal negativity peaked around 136 ms after target onset (*SD* = 27.5), with an average amplitude of -1.18 µV (*SD* = 5.40). Peak amplitude showed a marginal interaction effect of number of targets and response type, $F(1, 352) = 3.16$, $p = .077$, with greater amplitudes for double targets in saccade trials and greater amplitudes for single targets in manual response conditions, *Figure 4.12*.

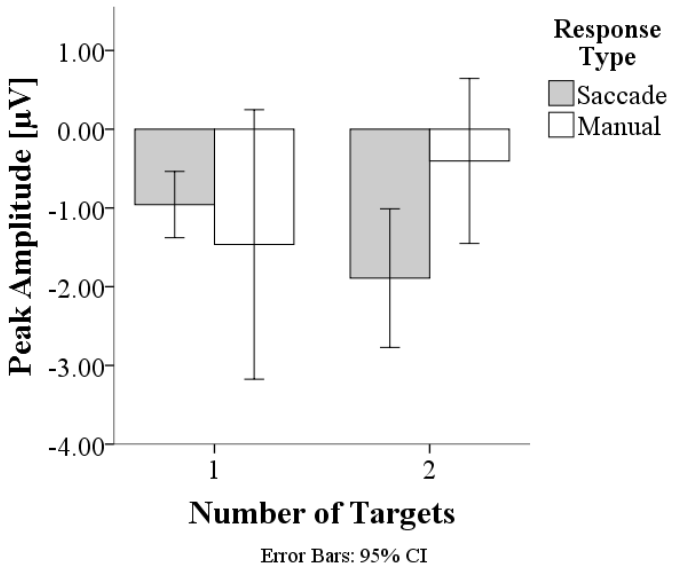


Figure 4.12. Interaction effect of number of targets and response type on frontal peak amplitude. Peak amplitudes are greater for double targets in overt attention shift conditions, while they are greater for single targets in manual response conditions.

Peak latencies showed significant main effects of number of targets, $F(1, 330) = 12.04$, $p < .001$, $d = 0.290$, with longer latencies for single ($M = 140$, $SD = 24.5$) than for double targets ($M = 132$, $SD = 29.7$), and of response type, $F(1, 330) = 22.64$, $p < .001$, $d = 0.405$, with longer latencies for saccades ($M = 142$, $SD = 27.7$) than for manual responses ($M = 130$, $SD = 26.2$). There was an interaction of target number and response type, $F(1, 330) = 8.30$, $p = .004$, with greater latency differences between response types for double than for single targets (*Figure 4.13*).

In summary, the frontal negativity had longer latencies for single than for double targets and longer latencies for saccades than for manual responses, especially in double target conditions.

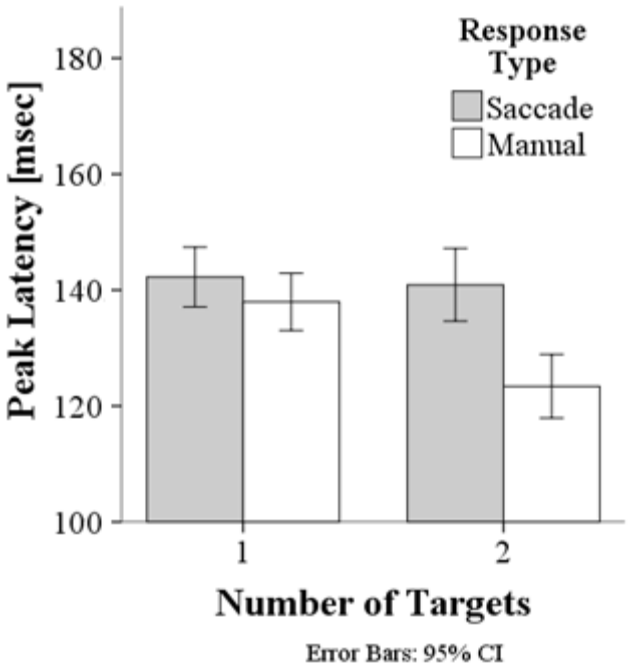


Figure 4.13. Interaction effect of target number and response type on frontal peak latency. Peak latencies are longer for saccades than for manual responses and this effect is greater for double targets than for single targets.

4.4 Discussion

This study aimed to investigate brain mechanisms of covert and overt attention shifts towards single and double targets. It was hypothesised that behavioural responses would be faster for saccades than for manual responses and faster towards single targets than towards double targets. On a neural level, a posterior positivity was expected to show greater amplitudes towards single than towards double targets. Fronto-central areas were expected to be involved in saccadic conditions but not for manual responses, while greater frontal inhibitory responses reflecting saccade inhibition were expected for manual responses.

4.4.1 Behavioural responses

As expected, behavioural response latencies were shorter in single than in double target conditions and shorter in saccade than in manual response conditions, in line with previous research comparing saccadic latencies with button press latencies (e.g. Bekkering et al., 1994; Bekkering et al., 1996; Briand et al., 2000). This confirms that neuromotor pathways involved in saccade execution are faster than those involved in hand movements. Longer reaction times towards double compared to single targets

may reflect additional processing effort required for the decision process when two targets are presented.

4.4.2 Neural responses

Neural responses included a small early posterior positivity followed by a later positivity and a frontal negativity. Manual response conditions furthermore showed a frontal positivity peaking towards the end of the extracted time window.

Early posterior positivity

The early posterior positivity peaked around 67 ms after target onset and showed larger amplitudes for single than for double targets. Decreases in visual response amplitudes with increasing numbers of stimuli are in line with previous research (Keitel et al., 2013; Moran & Desimone, 1985) and confirm the hypothesis. The latency of the early posterior response did not differ between conditions, suggesting that it is a mainly visual response that is unaffected by additional processing mechanisms related to the factors varying in this study.

Later posterior positivity

The posterior positivity peaked around 141 ms post stimulus. In line with the hypothesis, it had higher amplitudes in single than in double target conditions. The posterior positivity is similar to occipital responses observed in previous studies of covert attention shifts (e.g. Harter et al., 1982; Heinze et al., 1990; Luck et al., 1990; Mangun, 1995; Rugg et al., 1987). Higher response amplitudes towards single than towards double targets confirm previous findings using single cell recordings in non-human primates (Moran & Desimone, 1985) and steady-state visually evoked potential studies in humans (Keitel et al., 2013). The posterior response was lateralised only for single targets, with greater ipsilateral amplitudes, but not for double targets, confirming that it depends on the visual input. As electrical stimulation of lower V1 layers facilitates eye-movements (Schiller & Tehovnik, 2005), greater activation for single targets might result in the faster saccade latencies seen in this condition. As the early visual cortex projects to the superior colliculus (SC, Collins et al., 2005; Schiller & Tehovnik, 2005), stimulation of which elicits eye movements (Schiller & Stryker, 1972), occipital responses might directly influence SC activation. SC activation needs to reach a specific threshold for a saccade to be executed (Neggers et al., 2005). Hence, the

higher activation in occipital areas for single than for double targets might result in the threshold for saccade execution being reached earlier in SC, leading to shorter saccadic latencies for single than for double targets.

In regards to bottom-up attention shifts, this suggests that the neural response amplitude to a specific visual input can influence the speed of subsequent saccade execution, leading to quicker bottom-up attention shifts when the visual stimuli elicit greater responses. In bottom-up attention tasks distracting stimuli lead to slower response latencies towards targets, for example in visual search tasks with similar stimuli response times increase with set size (e.g. Wolfe, 1998; Wolfe, Cave, & Franzel, 1989; Woodman & Luck, 1999). In line with current findings on the occipital response amplitude, the decrease in response amplitude with increasing numbers of stimuli may result in slower attention shifts towards the stimuli, therefore increasing response latencies. The early posterior response in this study may be an earlier marker of successful attention shifts during visual search.

Response amplitudes did not significantly differ between covert and overt shift conditions. Therefore, the suggestion that saccade planning can enhance brain activity related to visual processing (Saber et al., 2015) was not confirmed in this study.

The response peaked earlier for double targets than for single targets and it peaked earlier for manual responses than for saccades. Manual responses and double target conditions are related to two different variable dimensions (response type and visual input). However, both involve an inhibition of an eye movement, either to both sides due to the instructions for the manual response condition (i.e. a general inhibition of all eye movements), or towards one of the stimuli for the double target condition. In manual response conditions a clear posterior negativity was visible towards the end of the extracted window (compare Appendix F). One explanation for the earlier peaking posterior positivity in double target conditions and in manual response conditions may be that their inhibition of eye-movement coincides with a posterior negativity that follows the positivity. Due to the overlap of both responses, the positivity peaks earlier and only lasts for a shorter time. In line with the idea of visual cortical areas activating SC to initiate saccades, this inhibitory response may be involved in inactivating SC to prevent eye movements. Double target conditions also showed smaller peak amplitudes, which is in line with this explanation, as the overlap with the subsequent negativity might also cause this decreased amplitude. The earlier posterior peak latency did not

coincide with faster behavioural responses; on the contrary behavioural responses were slower in conditions where the neural response peaked earlier. A possible explanation is that the amplitude needs to reach a certain threshold for response initiation, which would be in line with interpretations of amplitude differences. Due to the shorter early peak for manual responses and double target conditions, the threshold is not reached and more activation would be required to initiate saccades.

An alternative explanation would be that different mechanisms lead to a saccade initiation in single and double target conditions. In single target conditions the bottom-up target response (i.e. the response elicited in the visual cortex) is the most reliable source for information to shift towards the correct direction. Hence the visual response drives the fixation shift, indicated by high peak amplitudes in occipital areas. However, in double target conditions subjects can decide freely and therefore use top-down attentional mechanisms instead of visual cues to decide which target to shift to. Therefore, the visual response is smaller, while other responses may play a greater role for initiation of fixation shifts, possibly the frontal negativity which will be discussed in the following section.

Frontal negativity

The frontal negativity peaked significantly earlier for double targets than for single targets and for manual responses than for saccades. The latency was shortest in the manual double target condition, leading to an interaction effect of target number and response type. As manual responses and double target conditions both involve an inhibition of eye-movements, the earlier negativity might reflect additional processes for inhibition of saccades. The fact that manual double target conditions showed the shortest latencies corroborates this theory. As the frontal negativity peaks prior to the posterior negativity, it may be possible that frontal areas inhibit posterior areas to avoid their activation reaching the threshold to elicit an eye movement in SC. This would be in line with previous research suggesting that frontal areas (PFC and FEF) are involved in suppressing unwanted reflexive eye-movements (Miller, 2000; Rafal et al., 2000).

The frontal negativity had greater amplitudes for double targets in saccade trials and greater amplitudes for single targets in manual response conditions. If the frontal negativity indeed reflects saccade inhibition, the greater amplitude for double targets in saccadic trials shows that an eye movement to one of the two targets needs to be

inhibited in this condition. In manual response conditions eye movements generally need to be inhibited. For manual trials the frontal negativity is greater for single targets. In line with the collicular activation hypothesis stated above, the posterior response amplitude is greater to single than to double targets, meaning that greater inhibition is required to keep visual areas from activating SC to reach the saccade execution threshold. Hence, the greater frontal negativity may reflect stronger inhibition.

Alternatively the frontal negativity may be the other end of a dipole causing the posterior positivity. Both responses occur at a similar time; however, as the frontal negativity peaks slightly earlier (5 ms), a dipole cannot account for all the variations observed.

4.4.3 Cortical involvement in attention

Previous research on hemispherectomised infants showed that the cortex plays a crucial role for attention shifts when there are competing targets (Braddick et al., 1992). The current study confirms that different cortical processes can be measured with EEG during covert and overt attention shifts, involving occipital and frontal responses.

4.4.4 Differences between overt and covert attention shifts

In general, similar responses were found for overt and covert attention shifts. However, the posterior positivity was more widespread for overt than for covert attention shifts, possibly due to an earlier posterior negativity in covert attention shift trials. A frontal negativity peaked earlier for covert attention shifts and may be involved in initiating this posterior negativity. Both negativities may reflect inhibitory processes involved in the inhibition of eye movements. As visual areas can activate SC to initiate eye movements, the inhibitory responses may peak earlier to inhibit visual areas from reaching the required threshold. There were no striking differences in early response components between overt and covert shifts in fronto-central areas, as might have been expected due to saccade planning. This suggests that these preparatory processes may be more linked to the saccade onset than to the target offset and so not be visible when the extracted potentials were measured in relation to the target onset. However, manual response conditions showed a later frontal positivity occurring towards the end of the extracted time window, possibly reflecting inhibition of saccades.

4.4.5 Extraction of attention responses

The double target condition was introduced in this study to distinguish between visual and attentional responses. Behavioural responses were faster towards single than towards double targets, possibly due to additional processing effort required for multiple targets. In the EEG, the posterior positivity showed greater lateralisation for single targets than for double targets, suggesting that this response is at least partially related to visual input and most likely corresponds to visual signals in the occipital lobe. Posterior responses had higher amplitudes for single than for double targets, which, as discussed above, is in line with previous literature. Peak latencies of the occipital positivity and the frontal negativity were shorter for double targets than for single targets, possibly reflecting an overlap with negativities reflecting the inhibition of eye movements towards the unattended target.

4.4.6 Suitability of the method

The current study succeeded in measuring brain responses involved in both covert and overt shifts of attention by combining and co-registering eye tracking and EEG. Although MRI can be used to investigate covert and overt attention shifts (e.g. Corbetta et al., 1998), because of its low temporal resolution, eye movements can cause artefacts unless subjects are instructed to inhibit their over eye movements for a certain time (memory guided saccades) (e.g. Saber et al., 2015). EEG has a high temporal resolution, allowing selection of data from the period before saccade onset (in this case 180 ms from target onset onwards). This means that it is not required to instruct subjects to artificially delay or inhibit their saccades, but that data from the eye-tracker can be used to exclude responses that occur during eye movements. This leads to more natural saccades in response to stimuli and allows a detailed investigation of the time course of responses in different brain areas.

One caveat needing consideration when investigating overt attention shifts is that the regular potentials created by eye movements can result in artefacts in the ERP data if low pass filter settings are too high, as was clearly demonstrated with this data set in Appendix C. I therefore recommend using a high pass filter criterion of 0.01Hz for adult subjects, and extracting short time windows after target onset to avoid eye movement artefacts distorting the data.

The current study compared covert and overt attention shifts using the same stimuli and set up, ensuring a high consistency. The covert attention shift task was purposefully kept simple, to make it more comparable to the saccade task. However, it differs in difficulty from most previous EEG studies, as instead of a simple bottom-up-driven response to targets, these involved a top-down response (e.g. response to matching letters (Heinze et al., 1990), responses to specific target letters (Luck et al., 1990), or cueing of a specific location that leads to top down attention towards it (Mangun, 1995)). Therefore, the current study was able to mainly investigate bottom-up mechanisms of attention. In conclusion, it is possible to use combined eye-tracking and EEG to compare overt and covert bottom-up attention shifts.

4.4.7 Implications

The basis for the paradigm used in this study was the FSP, which can be used as a clinical diagnostic tool in non-verbal populations and infants (e.g. review: Atkinson & Braddick, 2012). Although the current study verbally instructed subjects to make eye movements in order to obtain informed consent, previous research shows that the same paradigm can be used without a need for verbal instruction. Therefore, this method is appropriate for patients with language impairments. The methodology developed in this chapter can therefore potentially be used to investigate neural mechanisms of attention shifts in infants and patients with language impairments.

4.4.8 Summary and conclusion

This chapter shows that it is possible to combine eye-tracking and EEG to compare overt and covert attention shift tasks. It compared covert attention shifts, which have been more commonly studied in the previous literature, with overt shifts, using the same task. Responses during overt and covert attention shifts were similar, allowing for a comparison of both tasks. However, frontal responses were more pronounced for covert shifts, possibly reflecting the inhibition of eye movements. Posterior positivities were greater for overt attention shift tasks and may contribute to the execution of saccadic eye movements via a pathway from visual cortex to SC. The current chapter established the overall pattern of neural responses during covert and overt attention shifts and demonstrated that it is possible to combine eye tracking and EEG to study them. The following chapters will investigate how overt attention shifts differ between competition and non-competition conditions in adults and infants.

Chapter 5 Cortical mechanisms of attention shifts during the FSP in adults

5.1 Study 1: Cortical mechanisms of attention shifts in adults

The previous chapter showed that brain mechanisms of overt attention shifts can be measured using combined eye-tracking and EEG, with a simplified version of a Fixation Shift Paradigm (FSP). However, the main interest of the FSP, both for neuroscience and for clinical studies has been the difference in saccade latencies between non-competition and competition conditions (Hood, 1995). In the experiments in this chapter, both non-competition and competition conditions were introduced, making the measure comparable to the FSP used in clinical and infant studies (reviews: Atkinson & Braddick, 2011; Atkinson & Braddick, 2012).

5.1.1 Attention in adulthood

Young adults between 20 and 30 years of age have superior attentional functions to children or older adults in different attentional tasks, including for example covert orienting of attention (e.g. Brodeur & Enns, 1997), voluntary shifts of attention in visual search (e.g. Trick & Enns, 1998) and sustained attention (e.g. McAvinue et al., 2012). This suggests that the brain mechanisms of attention at this age are most efficient to create successful behavioural patterns of attention. Studying these mechanisms of attention shifts can provide insights to the mechanisms that are commonly active in healthy adults. These can then be used as a comparison for mechanisms in patients or infants to investigate which mechanisms are driving the changes with age. Investigating brain correlates of attention in young adults can provide further insight to which state the brain should ideally develop from infancy to adulthood. Furthermore, adults are compliant subjects who can concentrate on attention tasks for longer than infants, leading to less noise in the data. Therefore, the experiments in this chapter aimed at investigating the neural mechanisms of attention shifts in healthy young adults as a basis for comparison with infants.

In the FSP adults show significantly shorter saccadic latencies than infants (Hood & Atkinson, 1993). However, the effects of different conditions are similar in adults and infants, as they both make slower saccades in the competition condition than in the non-competition condition and the fastest saccades in the gap condition (Csibra et al., 1997; Fischer, 1986; Hood & Atkinson, 1993; Saslow, 1967). Two explanations for

shorter latencies in non-competition and gap conditions in adults are, firstly, that in these conditions no disengagement is required, leading to accelerated responses or, secondly, that the gap or offset primes the system to make a faster response (Hood & Atkinson, 1993). The current study aimed at investigating the neural basis of attention shifts to shed further light on these alternative explanations.

5.1.2 Neural mechanisms of disengagement in adults

The previous chapter identified different prominent neural responses during the fixation shift, including a posterior positivity and a frontal negativity. As the task and stimuli used in this and the previous chapter are comparable, similar neural responses can be expected. The major addition to the previous chapter is the comparison of competition and non-competition conditions in the current chapter. To my knowledge, this is the first study to investigate neural mechanisms in the FSP using combined EEG and eye-tracking. However, Csibra et al. (1997) used the similar gap paradigm to study ERPs during attention shifts. They tested gap and overlap conditions, but not the non-competition condition. Brain responses (see Table 5.1 for a summary) identified by Csibra et al. (1997) included a prefrontal positivity in gap trials only, that preceded the target onset and was therefore suggested to be related to the offset of the fixation stimulus. A parietal positivity peaked 40 ms after target onset, having greater amplitudes in gap than in overlap trials. It was followed by a posterior positivity that peaked in the contralateral hemisphere first, followed by the ipsilateral one and had larger amplitudes in the gap than the overlap condition. Latency differences between conditions were not investigated in their study (Csibra et al., 1997). As they can provide valuable insights into the timing of responses, the current study aims to provide a more detailed analysis of attention shift responses and their latencies. Csibra et al. (1997) mentioned in their study that some responses might have overlapped with early saccades, as they averaged across all trials. As the current study combines eye-tracking with EEG, the eye tracking data was used to exclude trials with premature eye movements to avoid confounds with eye movement artefacts (see Chapter 2, section 2.3).

Table 5.1. *Summary of target-locked ERPs observed by Csibra et al. (1997) in the gap paradigm.*

Response	Timing	Variation between conditions
Prefrontal positivity	Preceding target onset	Appears in gap condition only
Parietal positivity	40 ms after target onset	Greater amplitudes in gap than in overlap trials
Posterior positivity	80 ms (contralateral) to 148 ms (ipsilateral)	Greater amplitudes in gap than in overlap trials

Csibra et al. (1997) additionally extracted event related potentials that were locked to the saccade, including a centro-parietal positivity peaking 8 ms before saccade onset, coinciding with an anterior ipsilateral negativity and an earlier parietal pre-saccadic positivity with higher amplitudes in overlap than in gap trials between 60 and 0 ms before saccade onset. These pre-saccadic potentials have been confirmed in adult studies using similar paradigms (Kawakubo et al., 2007; Moster & Philadethia, 1991). As discussed in Chapter 4, this thesis focuses on stimulus-locked ERPs but acknowledges that it is important to consider that stimulus-locked and saccade-locked ERPs might overlap and complement each other to form the mechanisms of attentional disengagement and fixation shifts. Neural models of attention (summarised in section 1.4.3 of Chapter 1) suggest that cortical areas including frontal, parietal and occipital regions, as well as the subcortical superior colliculus, may be involved in attention shifts involving disengagement.

5.1.3 Aims and hypotheses

This study aimed at combining eye-tracking and EEG with the FSP to monitor brain mechanisms of attention shifts in non-competition and competition conditions. As in the previous experiment, single and double target conditions were used to investigate which responses are more likely to be related to visual responses or to attention. In line with previous literature (Csibra et al., 1997; Fischer, 1986; Hood & Atkinson, 1993; Saslow, 1967), saccade latencies were expected to be shorter in the non-competition

condition than in the competition condition and, as in the previous chapter, shorter for single targets than for double targets.

ERPs were expected to show similar responses as in the previous chapter, including a posterior positivity and a frontal negativity. If the difference in saccade latency between competition and non-competition is caused by early neural mechanisms, the latencies of early brain responses should already show significant differences between conditions. In line with Csibra et al. (1997) the posterior response was expected to show higher amplitudes in non-competition than in competition conditions. If V1 activates SC, as suggested by Bronson (1974), response latencies in posterior areas should furthermore be shorter in non-competition conditions than in competition conditions.

5.2 Method 1

5.2.1 Participants

Twenty-seven students from the UCL Psychology subject pool (Mean age = 24.9 years, *SD* = 10.1, range = 18 to 58, 7 male, 24 right-handed) volunteered to participate in the study in exchange for course credit or monetary compensation (£10). One subject was excluded because of technical problems, one because of excessive noise in the EEG data, one because she did not complete the whole experiment and one because of a pre-diagnosed brain tumour. Remaining subjects all had normal or corrected to normal vision and no known history of brain disease. The study was approved by the UCL ethics committee (Ref. number: CPB/2013/011 and CPB/2014/007).

5.2.2 Materials and Stimuli

Stimuli were presented on a grey background with a mean luminance of 77 cd/m^2. The experiment began with the presentation of a first stimulus, a black schematic face, changing "expression" at a rate of 3 Hz and a green fixation dot, appearing in the centre of the screen. The dot had a size of 0.7 degrees of visual angle and the face subtended visual angle of 7.7° x 7.7°. The central dot and face remained visible for a randomised inter-trial interval between 0.5 and 2.5 seconds before the target appeared. Subjects were instructed to fixate on the central dot to avoid eye-movements between different positions on the face. When the subject fixated on the dot after the random

inter-trial interval, target stimuli were randomly presented on the left, right or on both sides of the screen at an eccentricity of 12.9° of visual angle. Target stimuli were bars made up of one black and one white rectangle that reversed colour at a rate of 3 reversals per second. In competition conditions the central face and the dot remained on the screen whereas in the non-competition condition, they both disappeared at the onset of the bars (*Figure 5.1*).

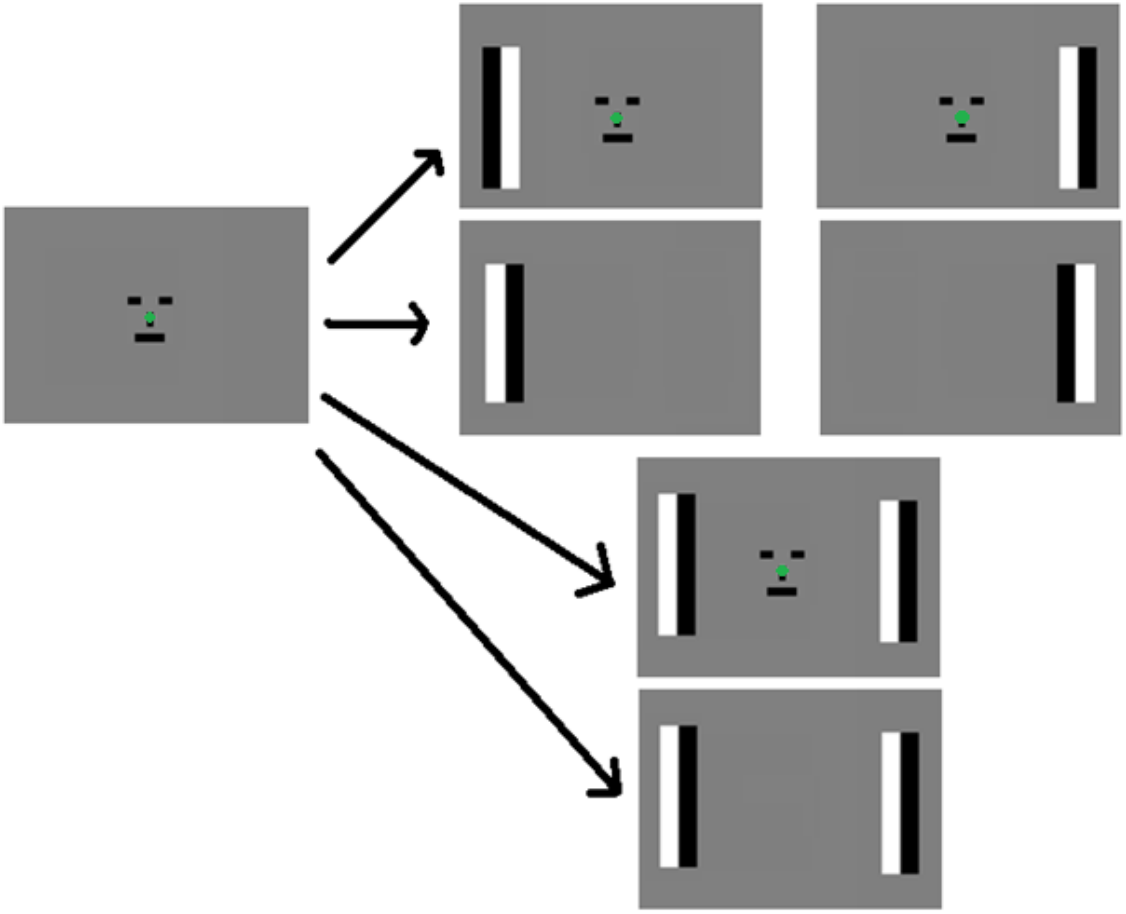


Figure 5.1. Stimuli used for study 1. Target displays in single target (top) and double target (bottom) conditions and with competition (central face visible) and non-competition (central face disappears) conditions.

5.2.3 Procedure

After the standard eye tracking calibration (see Chapter 2, section 2.2.2 for details), subjects were asked to focus on a central green dot and shift their focus to bars that randomly appeared on one or both sides of the screen. They were instructed to look left or right when bars appeared on both sides of the screen. When the peripheral bars disappeared, the subjects were asked to shift their focus back to the green dot. Short

breaks were given between each set of 100 trials, with a longer break occurring after 400 trials while the experimenter readjusted the electrode impedance. The entire experiment was composed of 800 trials, two thirds of which were single targets and one third double targets, and lasted for approximately an hour. Conditions were presented in a random order.

5.2.4 Design

For the behavioural analysis, a 2x2x2 within-subject design was used to investigate the effects of competition condition (competition or non-competition), screen side watched (left or right) and the number of peripheral targets (one or two) on saccade latency. For the neural analysis, the effects of competition condition (competition or non-competition), number of peripheral targets (one or two), brain hemisphere (ipsi- or contralateral brain hemisphere to the eye movement) and brain side (left or right side of the brain) on ERP amplitude and latency were determined. As in the previous chapter (Chapter 4, section 4.2.4), there were two measures for brain lateralisation: *brain hemisphere* describes the lateralisation in relation to the target (hemisphere ipsi- or contralateral to the stimulus that was reacted to) and the factor *brain side* compares the left and right side of the brain.

5.3 Results 1

5.3.1 Data processing

The methodology chapter describes the detailed methods used for processing eye-tracking and EEG data (see Chapter 2, section 2.2.3 and 2.3). On average, 8.6% (*SD* = 3.0%) of trials were interpolated across all subject, with all subjects having less than 14.4% interpolated trials. The individually calculated noise threshold for ERP samples was 13.7 µV (*SD* = 3.94 µV), and the individually calculated range threshold within epochs was on average 53.8 µV (*SD* = 14.0 µV). The average number of trials subjects successfully completed behaviourally was 766 (*SD* = 48.6). After exclusion of noisy EEG data, an average of 703 (*SD* = 55.9) trials remained in the analysis.

5.3.2 Behavioural results

The eye tracking data quality was high with 98.0% correct re-fixations, only 1% noisy data and 0% sticky fixations. In single target trials 1.5% of saccades were directed

to the wrong direction, 1.2 % misdirected saccades that were subsequently corrected (80% of the initially misdirected saccades).

Saccade latencies (M = 0.309 sec, SD = 0.161) were analysed using a mixed linear model including participants as a random effect and screen side, condition and number of stimuli as fixed factors. It showed significant main effects of condition, $F(1, 19001) = 164.81$, $p < .001$, $d = 0.198$, and number of targets, $F(1, 19001) = 71.95$, $p < .001$, $d = 0.128$. There was a significant interaction effect of screen side and number of targets, $F(1, 19017) = 20.12$, $p < .001$, with shorter latencies to the left side for single targets, but to the right side for double targets, and a significant interaction of condition and number of targets, $F(1, 19001) = 4.17$, $p = .041$, *Figure 5.2*. Latencies were shorter in the non-competition condition (M = 0.293 sec, SD = 0.171) than in the competition condition (M = 0.325 sec, SD = 0.151) and shorter for single targets (M = 0.302 sec, SD = 0.141) than for double targets (M = 0.324 sec, SD = 0.196).

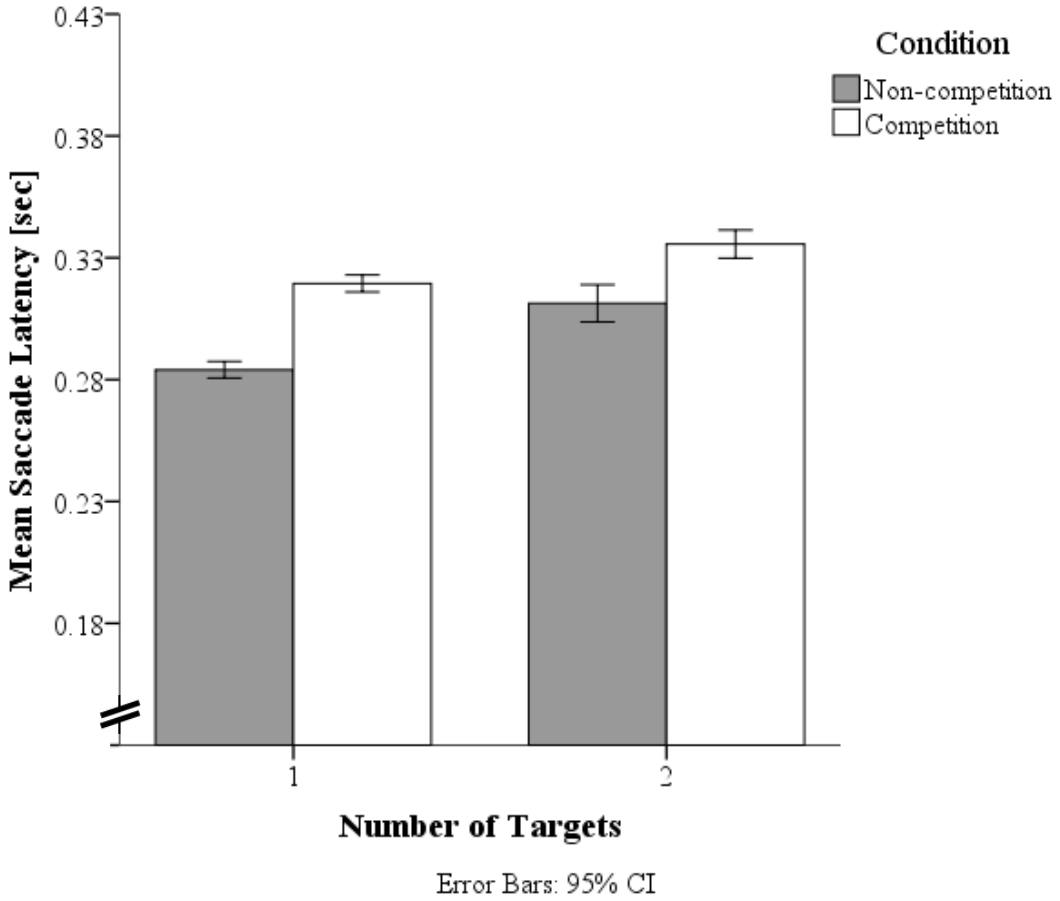


Figure 5.2. Interaction effect of condition and number of targets on saccade latency. Latencies are shorter in the non-competition conditions than in the competition condition and this effect is greater for single than for double targets.

In summary, saccade latencies were shorter in non-competition than in competition conditions and shorter for single targets than for double targets, especially towards the left screen side.

5.3.3 EEG Results

Full detailed topographical plots of the neural responses in non-competition and competition conditions are displayed in Appendix G, with selected time intervals in *Figure 5.3* and *Figure 5.4*. They show a small contralateral positivity in posterior areas that is followed by a greater posterior positivity that moves to the ipsilateral side and coincides with a frontal negativity (*Figure 5.3*). The occipital positivity is followed by a posterior negativity, peaking toward the end of the extracted time window. In double target trials a frontal positivity appears towards the end of the extracted time window (*Figure 5.4*).

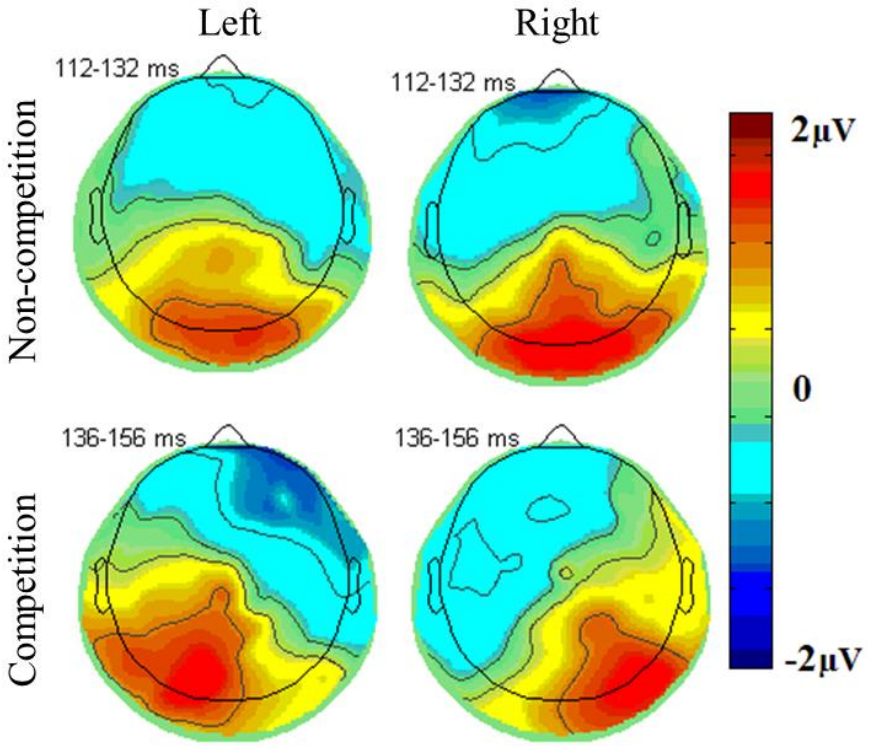


Figure 5.3. Topographical plots of the posterior response. Plots are displayed for single targets on the left (left plots) and right (right plots) side of the screen for non-competition (top) and competition conditions (bottom). The peak activity (displayed here) occurs earlier in the non-competition (112-132 ms) than in the competition condition (136-156 ms). Scale: -2 µV (blue) to 2 µV (red).

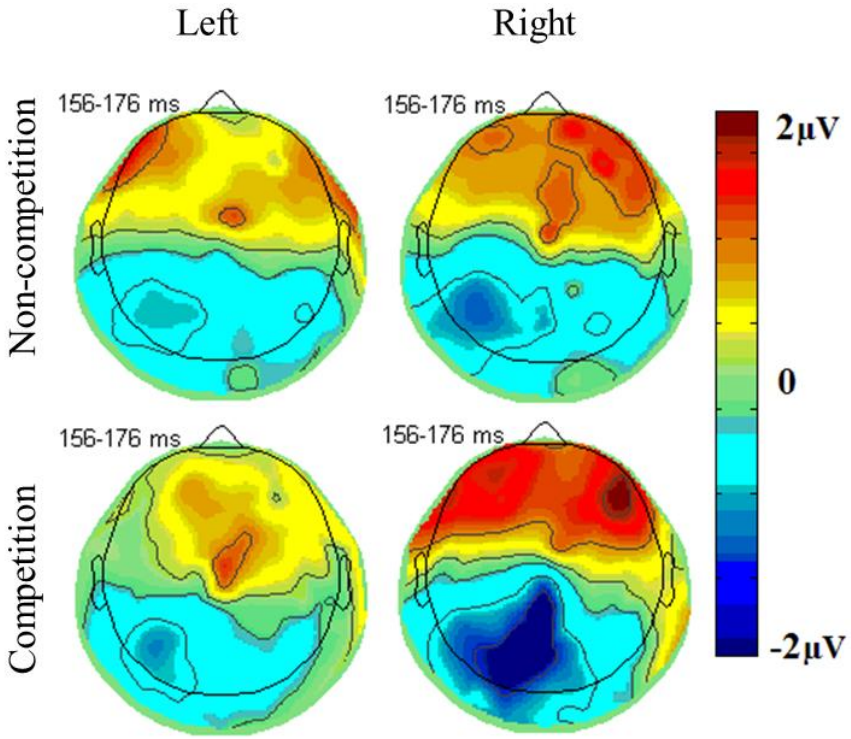


Figure 5.4. Topographical plots of later responses. In double target conditions the posterior positivity is followed by a negativity, coinciding with a frontal positivity. Displayed are double target trials in which subjects subsequently looked at the left (left plots) and right (right plots) stimulus in non-competition (top) and competition (bottom) conditions. Scale: -2 µV (blue) to 2 µV (red).

Linear mixed models including participants as a random effect were calculated to predict amplitudes and latencies from condition, number of targets, brain hemisphere (ipsi- or contralateral) and brain side (left or right). In the following, amplitudes are displayed in µV, latencies are reported in ms.

Posterior responses

Responses were extracted in two electrode clusters around the occipital electrode locations O1 and O2 (see Chapter 2, Figure 2.4 and Section 2.3.2 for details on the extracted electrodes). The wave plots of lateral posterior regions show a small early posterior positivity peaking between 40-90 ms after target onset, followed by a greater peak between 110-180 ms (*Figure 5.5* and *Figure 5.6*).

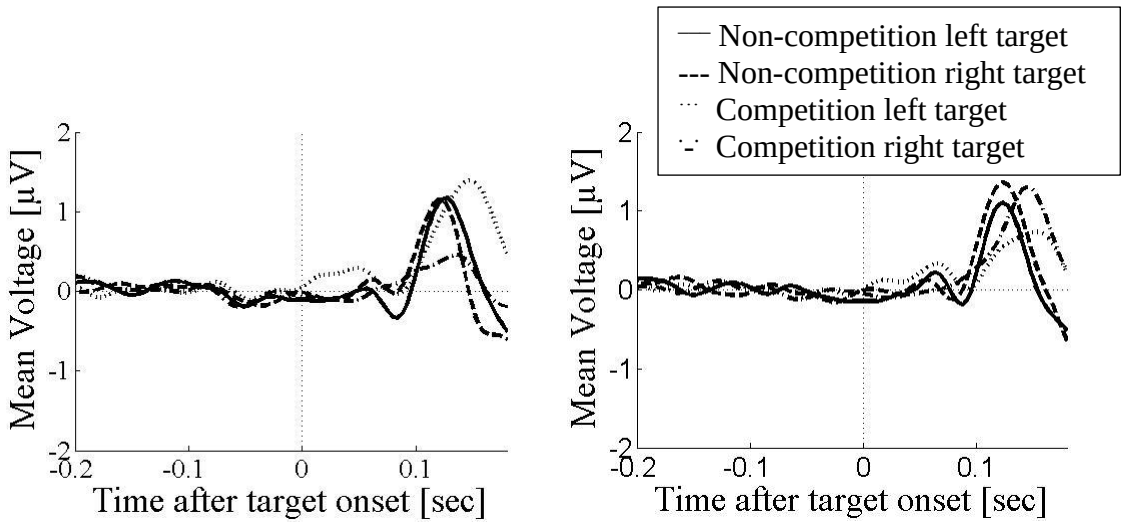


Figure 5.5. Occipital wave plots for single targets. Responses to single targets in the left hemisphere (left) and the right hemisphere (right) of the brain are displayed.

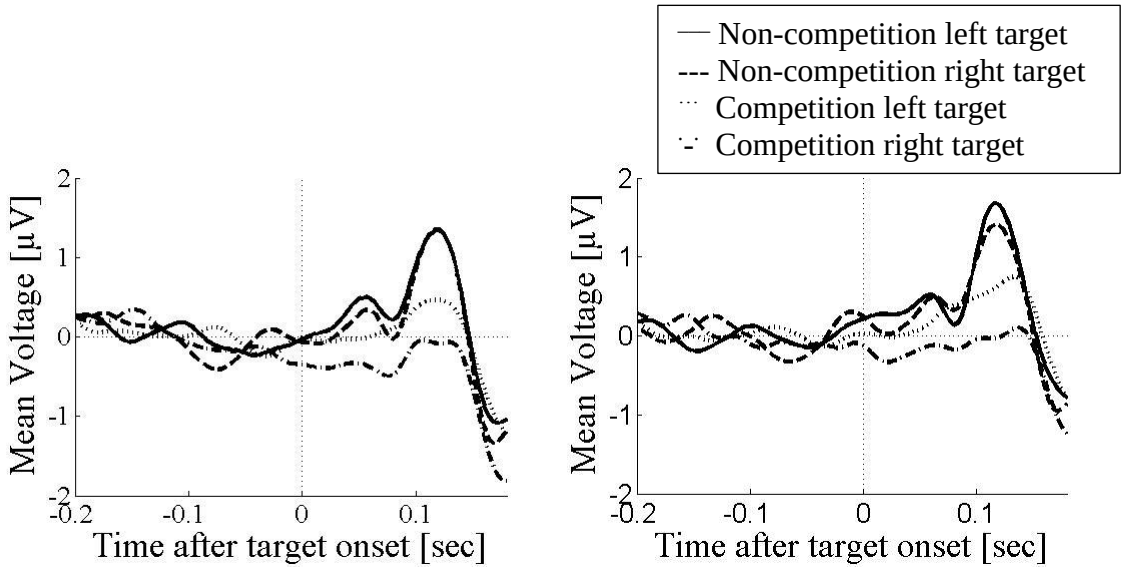


Figure 5.6. Occipital wave plots for double targets. Responses to double targets in the left hemisphere (left) and right hemisphere (right) of the brain are displayed.

Early posterior positivity

The early posterior positivity peaked after 68.1 ms (*SD* = 20.6) with an average amplitude of 0.43 µV (*SD* = 2.22 µV). Peak amplitude showed a significant effect of condition, $F(1, 345) = 4.47$, $p = .035$, $d = 0.200$, with higher amplitudes in the non-competition ($M = 0.65$, $SD = 2.10$) than in the competition condition ($M = 0.21$, $SD = 2.31$). Separate analyses for single and double targets confirmed this effect for double targets, $F(1, 161) = 5.35$, $p = .022$, $d = 0.296$, with higher amplitudes in the non-competition ($M = 0.80$, $SD = 2.09$) than in the competition condition ($M = 0.08$, $SD = 2.70$), while the effect was not significant for single targets, $F(1, 161) = 0.50$, $p = .481$,

d = 0.084, although amplitudes were also higher for non-competition (*M* = 0.50, *SD* = 2.10) than for competition conditions (*M* = 0.33, *SD* = 1.85).

Peak latencies showed a significant three-way interaction effect of number of targets, brain hemisphere (ipsilateral or contralateral to the saccade) and brain side (left or right), $F(1, 345) = 9.11$, $p = .003$. Separate analyses for single and double targets showed a significant interaction of hemisphere and brain side for single targets, $F(1, 161) = 4.94$, $p = .028$, with earlier peaks in the right hemisphere when it was contralateral but earlier peaks in the left hemisphere when it was ipsilateral. Double targets showed an interaction effect of brain hemisphere and side, $F(1, 161) = 4.33$, $p = .039$, in the opposite direction with shorter latencies in the left hemisphere when it was contralateral and in the right hemisphere when it was ipsilateral (*Figure 5.7*).

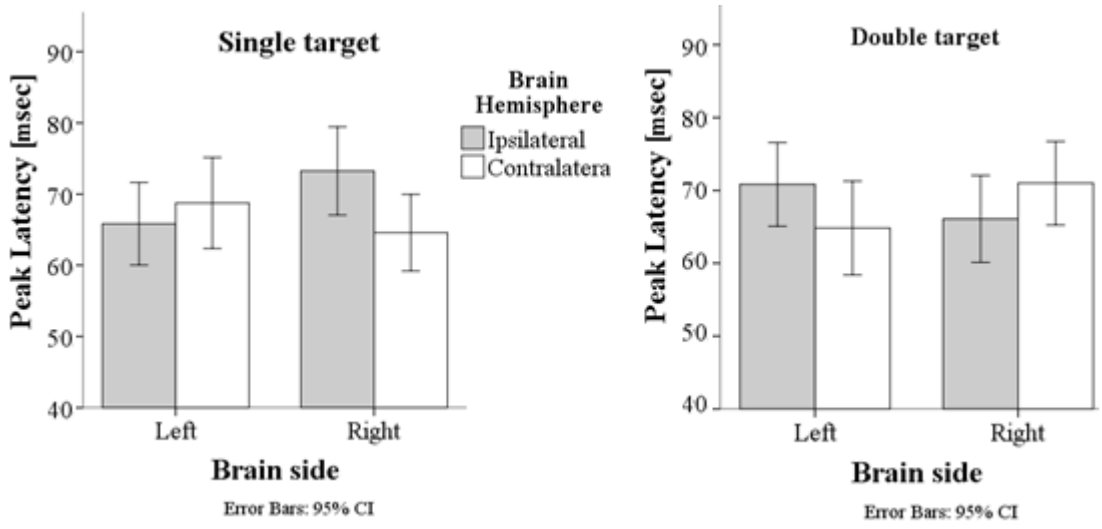


Figure 5.7. Three way interaction effect of brain side, hemisphere and number of targets on occipital peak latency. The interaction effect of brain side and hemisphere on peak latency differs between single and double target conditions.

In summary, double targets elicited greater early posterior peak amplitudes in the non-competition than in the competition condition. Peak latencies differed in lateralisation between single and double targets.

Later occipital positivity

The later posterior positivity peaked around 130 ms (*SD* = 23.7) and had an average amplitude of 0.85 µV (*SD* = 3.49 µV). Peak amplitude showed a significant effect of condition, $F(1, 345) = 5.89$, $p = .016$, $d = 0.217$, with higher amplitudes in the non-competition (*M* = 1.38, *SD* = 2.97) than in the competition condition (*M* = 0.72, *SD* = 3.11) and a marginal interaction of condition and number of targets, $F(1, 345) = 3.51$, $p = .062$, *Figure 5.8*. Separate analyses for single and double target conditions confirmed the significant effect of condition for double targets, $F(1, 161) = 7.59$, $p = .007$, $d = 0.339$, with greater amplitudes in non-competition (*M* = 1.43, *SD* = 3.04) than in competition conditions (*M* = 0.26, *SD* = 3.82), but not for single targets, $F(1, 161) = 0.23$, $p = .630$. No other effects were significant.

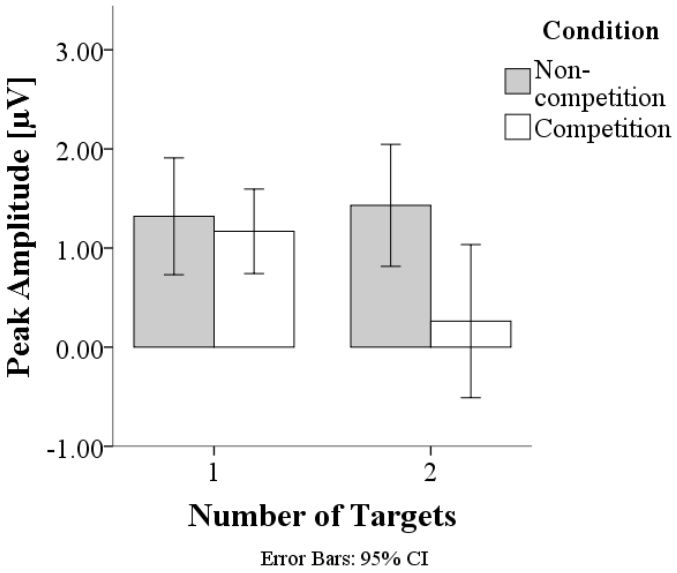


Figure 5.8. Marginal interaction effect of number of targets and condition on posterior peak amplitude. Amplitude differences between non-competition and competition conditions are greater for double targets than for single targets.

Peak latency showed a significant main effect of condition, $F(1, 345) = 23.31$, $p < .001$, $d = .426$, with shorter latencies in the non-competition (*M* = 125, *SD* = 20.5) than in the competition condition (*M* = 134, *SD* = 25.7), and a significant effect of number of targets, $F(1, 345) = 20.08$, $p < .001$, $d = 0.390$, with longer latencies for single targets (*M* = 135, *SD* = 22.9) than for double targets (*M* = 125, *SD* = 23.7). There was a significant interaction effect of condition and number of targets, $F(1, 345) = 8.70$, $p = .003$, *Figure 5.9*.

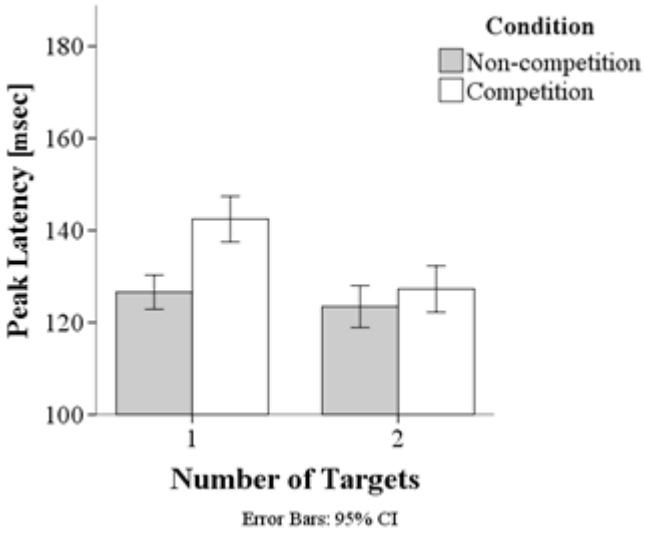


Figure 5.9. Interaction effect of number of targets and condition on posterior peak latency. Peak latencies are shorter in non-competition conditions than in competition conditions and this difference is greater for single targets than for double targets.

Separate analyses for single and double target conditions confirmed a significant effect of condition for single targets, $F(1, 161) = 29.28$, $p < .001$, $d = 0.757$, with shorter latencies in the non-competition condition ($M = 126$, $SD = 18.2$) than in the competition condition ($M = 143$, $SD = 24.4$), but not for double targets, $F(1, 161) = 2.01$, $p = .158$. Single target conditions showed a marginal effect of hemisphere on peak latency, $F(1, 161) = 3.36$, $p = .069$, $d = 0.051$, with longer latencies in the ipsilateral ($M = 126$, $SD = 23.8$) than in the contralateral hemisphere ($M = 125$, $SD = 23.7$), and a non-significant interaction of hemisphere and brain side, $F(1, 161) = 2.86$, $p = .093$, showing greater latency differences for the left than for the right side of the brain, *Figure 5.10*.

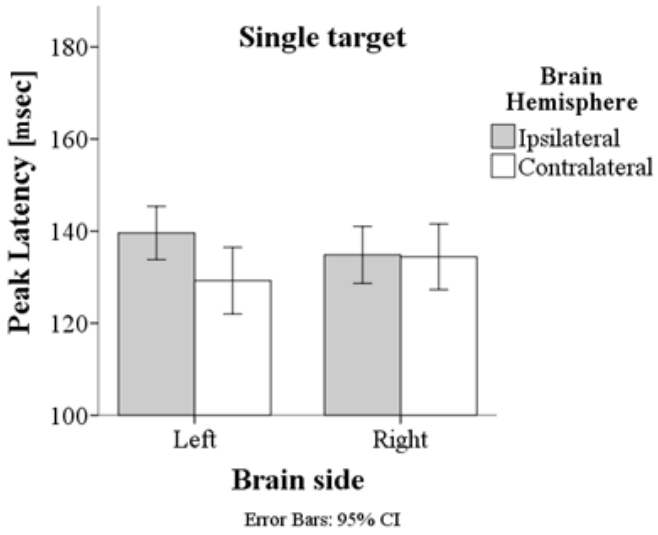


Figure 5.10. Interaction effect of brain side and hemisphere on posterior peak latencies. Peak latencies are shorter in the contralateral than in the ipsilateral hemisphere for the left brain side but not for the right brain side.

Double target conditions showed a significant effect of brain side on peak latency, $F(1, 161) = 6.39$, $p = .012$, $d = 0.289$, with shorter latencies in the left ($M = 122$, $SD = 21.7$) than in the right brain side ($M = 129$, $SD = 25.2$), and an interaction of condition and hemisphere, $F(1, 161) = 4.01$, $p = .047$, showing an earlier contralateral peak for competition conditions, but not for non-competition conditions (*Figure 5.11*).

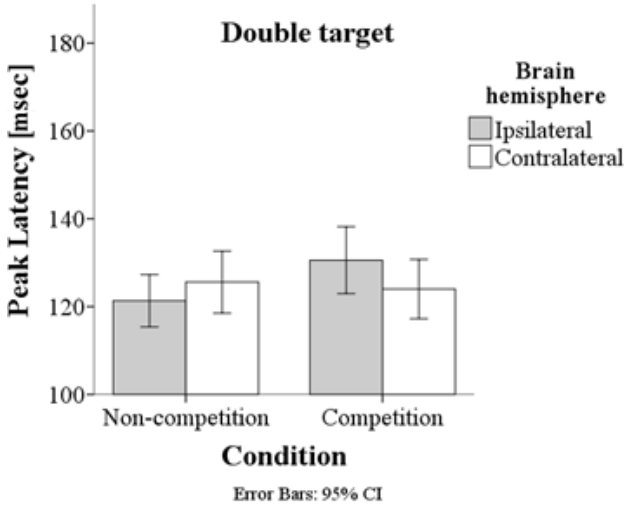


Figure 5.11. Interaction effect of condition and brain hemisphere on peak latency in double target conditions. The response has shorter latencies in the non-competition condition than in the competition condition in the ipsilateral but not in the contralateral hemisphere.

In summary, amplitudes of the later occipital response were greater in non-competition than in competition conditions, particularly for double targets. Peak latencies were shorter in the non-competition condition than in the competition condition, particularly for single targets. Latencies were longer for single than for double targets and single targets showed an earlier contralateral peak that moved to the ipsilateral hemisphere, while this lateralisation was only observed in competition conditions for double targets.

Frontal responses

Frontal responses were extracted in two lateral fronto-central electrode clusters (see Chapter 2, Figure 2.5 and section 2.3.2 for details on the extracted electrodes). Wave plots of frontal areas (*Figure 5.12* and *Figure 5.13*) show a small frontal positivity, peaking around 80 ms after target onset for single targets in non-competition conditions only and only in the contralateral hemisphere. It is followed by a greater frontal negativity, which is followed by a positivity that peaks outside the extracted time window.

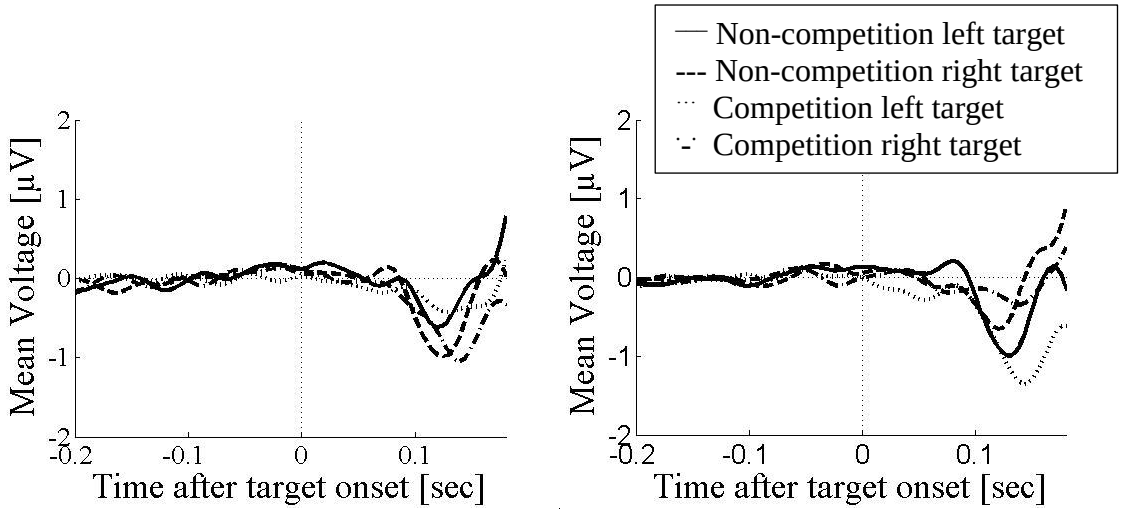


Figure 5.12. Frontal wave plots for single target conditions. Responses to single targets in the left hemisphere (left) and the right hemisphere (right) of the brain are displayed.

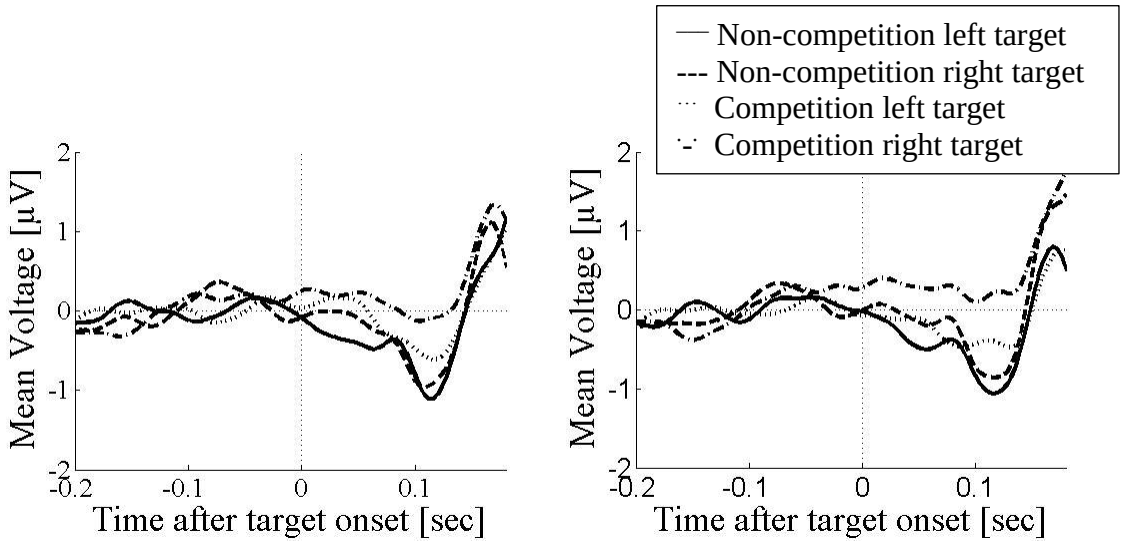


Figure 5.13. Frontal wave plots for double target conditions. Responses to double targets in the left hemisphere (left) and the right hemisphere (right) of the brain are displayed.

Frontal negativity

The frontal negativity peaked at 131 ms (*SD* = 24.5) and had an average amplitude of -1.69 µV (*SD* = 7.40 µV). Peak amplitude showed a marginal effect of brain hemisphere, $F(1, 345) = 3.35$, $p = .068$, $d = 0.141$, with smaller amplitudes in the ipsilateral (*M* = -1.01, *SD* = 4.16) than in the contralateral hemisphere (*M* = -2.00, *SD* = 9.04) and a significant interaction of hemisphere and brain side, $F(1, 345) = 6.80$, $p = .009$, *Figure 5.14*. Separate analyses for single and double targets confirmed the interaction of brain hemisphere and side for double targets, $F(1. 161) = 8.21$, $p = .005$, but not for single targets, $F(1, 184) = 1.91$, $p = .169$.

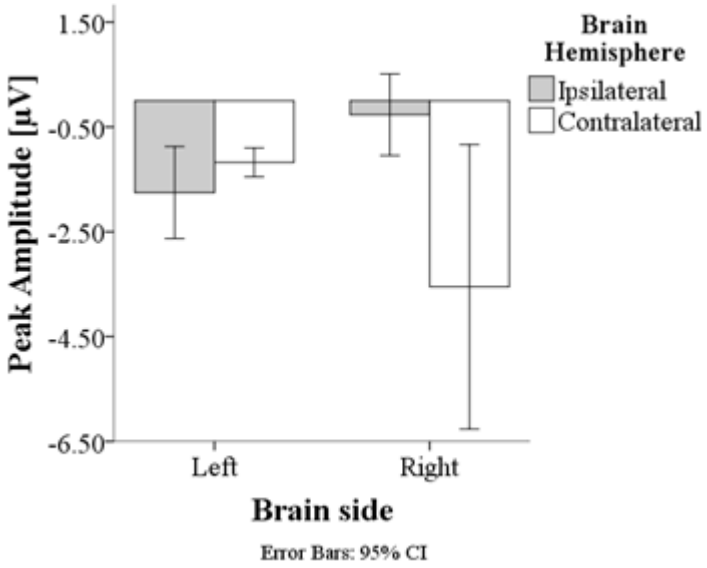


Figure 5.14. Interaction effect of brain side and hemisphere on frontal peak amplitude. Peak amplitudes in the right brain hemisphere are greater when it is the contralateral, than when it is the ipsilateral hemisphere, but this effect does not occur in the left hemisphere.

Peak latency showed significant effects of condition, $F(1, 345) = 17.50$, $p < .001$, $d = 0.348$, with shorter latencies in the non-competition ($M = 127$, $SD = 26.0$) than in the competition condition ($M = 136$, $SD = 26.3$), number of targets, $F(1, 345) = 14.85$, $p < .001$, $d = 0.317$, with longer latencies for single ($M = 136$, $SD = 25.3$), than for double targets ($M = 128$, $SD = 27.1$), and hemisphere, $F(1, 345) = 15.45$, $p < .001$, $d = 0.325$, with shorter latencies in the ipsilateral ($M = 128$, $SD = 24.5$), than in the contralateral hemisphere ($M = 136$, $SD = 27.8$). Furthermore, there were interactions of condition and number of targets, $F(1, 345) = 5.31$, $p = .022$, with greater latency differences between conditions for single targets than for double targets, and a marginal interaction of hemisphere and brain side, $F(1, 345) = 2.97$, $p = .086$, with greater latency differences in the right side of the brain than in the left side, *Figure 5.15*.

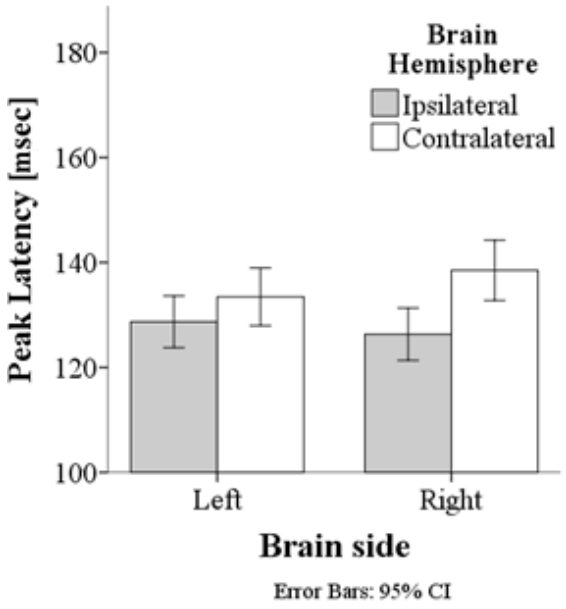


Figure 5.15. Interaction effect of brain side and hemisphere on frontal peak latency. The response peaks in the ipsilateral hemisphere first, followed by the contralateral hemisphere. The latency difference is greater in the right brain side than in the left.

Separate analyses for single and double targets confirmed a significant effect of condition on peak latency for single targets, $F(1, 161) = 24.46$, $p < .001$, but not for double targets. The effect of hemisphere on peak amplitude was confirmed for both single, $F(1, 161) = 13.95$, $p < .001$, $d = 0.427$, and double targets, $F(1, 161) = 4.29$, $p = .040$, $d = 0.238$, showing earlier peaks in the ipsilateral (single: $M = 130$, $SD = 24.0$, double: $M = 124$, $SD = 24.7$) than in the contralateral hemisphere (single: $M = 141$, $SD = 25.6$, double: $M = 131$, $SD = 29.0$).

In summary, peak amplitudes were smaller in the ipsilateral than in the contralateral hemisphere, especially in the right side of the brain for double targets. Peak latencies were longer in competition than in non-competition conditions, particularly for single targets. Latencies were longer for single than for double targets. The response peaked in the contralateral hemisphere first, followed by the ipsilateral hemisphere and this lateralisation was more pronounced in the right side of the brain.

5.4 Discussion: Experiment 1

The aim of this study was to monitor behavioural and neural mechanisms of attention shifts in competition and non-competition conditions of the FSP in adult subjects.

5.4.1 Behavioural results

Saccade latencies were significantly longer in the competition than in the non-competition condition, confirming the hypothesis and replicating previous studies comparing saccadic shifts either involving disengagement or no disengagement (Csibra et al., 1997; Fischer, 1986; Hood & Atkinson, 1993; Saslow, 1967). These findings confirm that additional processing time is required to disengage from a stimulus that is reflected in longer latencies.

Saccade latencies were significantly shorter for single than for double targets, confirming the hypothesis and replicating findings from the previous chapter. This suggests that subjects require additional time to shift if more targets are present. The latency increase may be caused by additional processing effort required for the choice between multiple stimuli and the need to inhibit orienting responses towards one of them.

5.4.2 Neural responses

Neural responses in the current study involved an early and a later posterior positivity and a later frontal negativity. Table 5.2 summarises the findings and contrasts them with previous research on brain responses during attention shifts in the gap paradigm (Csibra et al., 1997). The following sections will discuss the current findings in more detail.

Table 5.2. *Comparison of target-locked ERPs observed by Csibra et al. (1997) in the gap paradigm and in the FSP used in the current study.*

Response	***Csibra et al. (1997)***	**Current study**	**Explanation**
Prefrontal positivity preceding target onset in gap condition only	Yes	No	As the response precedes the target onset it is only visible in gap conditions.
Parietal positivity 40 ms after target onset with greater amplitudes in gap condition	Yes	No	Due to the early onset this response may also be related to the gap rather than the target onset.
Posterior positivity moving from contralateral to ipsilateral hemisphere with smaller amplitudes in competition conditions	Yes	Yes	As the response consistently occurs in all conditions (gap and non-competition), it is likely to be related to general attention shifts.
Early posterior positivity greater in non-competition condition	No	Yes	This may reflect an earlier visual response that was not detected by Csibra et al. (1997) because they averaged amplitudes across a wider time window.
Frontal negativity with no differences between conditions	No	Yes	This response may be the other end of the dipole causing the posterior response. Alternatively, it may reflect general attentional mechanisms that do not differ between conditions.

Early posterior positivity

The early posterior response showed greater peak amplitudes in non-competition conditions than in competition conditions, particularly for double targets. This is line with our hypothesis and previous research by Csibra et al. (1997). In the non-competition condition only one stimulus is visible while in the competition condition

two stimuli are presented. Therefore, the decrease in amplitude with number of stimuli is in line with findings from the previous chapter, as well as with previous single cell recording data from non-human primates (Moran & Desimone, 1985) and steady-state visually evoked potential data from humans (Keitel et al., 2013).

When only single target conditions were analysed this effect was no longer significant. For single target conditions the additional stimulus in non-competition trials is located in the *foveated* area, while another *peripheral* stimulus influences the response in the double target condition. The difference in the observed effects may indicate that the stimulus position might play a crucial role for the decrease of responses with target number.

The latency of the early response showed an interaction of brain side, brain hemisphere and number of targets, suggesting that the timing of the response differs for single and double targets. This suggests that different mechanisms are involved in single and double target tasks. Corbetta and Shulman (2002, 2011) suggested a right-lateralised pathway to be involved in attention shifts. This pathway may have a different role for double target conditions requiring additional control, leading to the different activation patterns observed in this study.

Late Posterior positivity

The amplitude of the later positivity showed the same pattern that was previously observed for the early positivity, with greater amplitudes in the non-competition than in the competition conditions, particularly for double targets. This is in line with the previous explanations, suggesting that split processing capacity between different targets decreases activation towards each of them. Brain side had no effect on this response, indicating that, as suggested by Corbetta and Shulman (2002, 2011) the occipital cortex is part of a bilateral network that is not right-lateralised.

Peak latencies were significantly shorter in the non-competition than in the competition condition, reflecting the significant difference that was found for saccade latencies and therefore suggesting that already early brain responses vary between conditions. The effect was more pronounced for single targets, possibly due to an overlap with subsequent negative components in double target conditions, as discussed in the previous chapter (Chapter 4, section 4.4.2).

Peak latencies were significantly shorter in double than in single target conditions, replicating the findings of the previous chapter. As suggested in Chapter 4, an overlap of the response with subsequent negative responses reflecting inhibition of one of the targets might lead to an earlier peak. There was a significant difference between latencies in non-competition and competition conditions, which is in line with this hypothesis.

In single target conditions there was furthermore an effect of hemisphere with shorter latencies in the contralateral than in the ipsilateral hemisphere. This effect is in line with findings from the previous chapter and with previous EEG papers (Csibra et al., 1997; Rugg et al., 1987), suggesting that the shift of the response from contralateral to ipsilateral sites is a robust finding. It is possible that interhemispheric connections play a crucial role for this shift of neural responses, possibly due to the contralateral area activating ipsilateral areas. As connections are impaired in some subject groups who struggle with the FSP, for example people with autism (Elison et al., 2013) and neglect patients (Bartolomeo et al., 2007; De Schotten et al., 2005), the response sequence from contra- to ipsilateral might play a crucial role in shifts of attention.

Frontal negativity

Peak amplitudes were smaller in the ipsilateral than in the contralateral hemisphere, similar to the pattern observed for the occipital positivity. The frontal negativity may be the other end of the dipole inducing the posterior positivity.

Double targets showed an interaction effect of brain side and hemisphere, with greater contralateral amplitudes in the right hemisphere than in the left hemisphere. Greater involvement of the right hemisphere has been suggested by several neural models of attention (Corbetta & Shulman, 2002, 2011). This finding suggests that the right-lateralised ventral network suggested by Corbetta and Shulman (2002, 2011) may be less involved in simple attentional shifts, but more involved in attentional shifts that require a certain control or disengagement, induced by double targets.

Peak latencies were significantly shorter in the non-competition condition than in the competition condition and significantly longer for single than for double targets. This is a similar pattern as observed for the posterior positivity in this study, suggesting that there are similarities in the response latency variation between conditions. Separate

analyses show that latency differences between competition and non-competition conditions are greater in the single than in the double target condition. The double target condition requires a voluntary decision, which side to attend to compared to the single target condition, where no such decision is required. It is possible that the decision elicits an additional response that overlaps with other responses and therefore partially masks the effect of latency difference between competition and non-competition conditions, making it less visible than for single target trials.

In addition, the frontal negativity peaked in the ipsilateral hemisphere first, followed by the contralateral hemisphere for both single and double targets. This, again, mirrors the pattern that was also observed for the occipital response, being in line with the alternative idea that the frontal negativity may be the other end of a dipole causing the posterior positivity.

5.4.3 Summary and interim conclusion

In summary, the current study identified brain responses similar to the ones established for the saccade condition in Chapter 4, replicating previous findings. There were significant latency differences between non-competition and competition conditions for the occipital positivity, and the frontal negativity paralleling the behavioural pattern of shorter saccade latencies in non-competition than in competition conditions. This suggests that conditions already differ on an early neural level within milliseconds after target onset. Considering that brain areas interact and activate each other, an early delay may lead to greater difficulties later on. It is possible that the differences are caused by differences in early visual responses to the different visual inputs or by attentional mechanisms and saccade preparation. The non-competition condition and competition condition differ in the central stimulus either disappearing or remaining visible at target onset. The offset of a visual stimulus can induce neural responses (Gomez et al., 1996; Vassilev, Manahilov, & Mitov, 1983), which may overlap with responses to the onset of peripheral targets and attentional responses. To investigate the role of the visual offset of the central stimulus on the identified neural differences between conditions, another experiment was conducted.

5.5 Study 2: The contribution of the offset response to brain mechanisms

5.5.1 Offset responses

The offset of a stimulus can elicit an event-related potential (ERP) response, the offset response. This response can be similar to early P1 and N1 responses elicited by the appearance of a stimulus (Gomez et al., 1996; Vassilev et al., 1983), or instead modulate later components (Csibra et al., 1997; Klotz & Ansorge, 2007). The magnitude of offset responses depends on stimulus features. For example it decreases with an increase in spatial frequency of visual stimuli (Vassilev et al., 1983), suggesting that it cannot be generalised across studies. Therefore, the aim of this study was to determine the offset response to the stimuli used in study 1, and whether these purely visual responses contribute to the differences observed between competition and non-competition conditions.

5.5.2 Additivity of neural responses

Temporally coinciding ERP components sum together to form the response that can be measured on the scalp (reviews e.g. Luck, 2005; Regan, 1989). Depending on the amount of overlap, the maximum of the merged response can lie between the two components (*Figure 5.16*). In the previous study, the peak latency of the posterior positivity was shorter in the non-competition condition than in the competition condition. The non-competition condition contains an offset of the central face instantaneously with the onset of the peripheral target. The earlier response measured under non-competition conditions may include an earlier offset response overlapping with the response to the onset of a peripheral target leading to a combined response that peaks earlier.

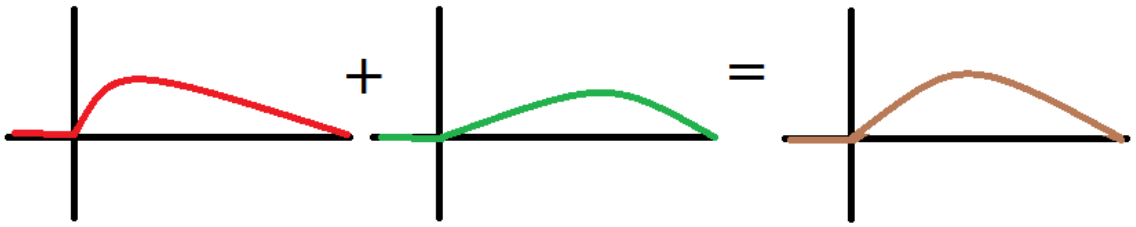


Figure 5.16. Schematic representation of two coinciding ERP components adding up to one visible response.

5.5.3 Aims and hypotheses

To examine whether peak latency differences detected between competition and non-competition conditions were confounded with the offset response, this study aimed to investigate the effect of the offset response to the face on the previously measured responses. Participants were therefore presented both with non-competition conditions and conditions in which the face disappeared while no peripheral bars appeared (offset condition). If the offset itself creates an ERP, this response should be visible in the face offset condition. Subtracting it from the non-competition condition can provide insights to the magnitude of the offset response on the responses. If the offset significantly affects the brain responses, it may be driving the effect observed in study 1.

A visual offset response similar to the ones previously observed (Gomez et al., 1996; Vassilev et al., 1983) was expected to partially affect the observed responses in non-competition conditions, in particular visual responses. However, it was predicted that the offset response cannot explain all observed differences between non-competition and competition conditions, as other processes including disengagement and saccade preparation are involved in the faster ERP latencies in non-competition than in competition conditions.

5.6 Method 2

5.6.1 Participants

Fourteen additional students from the UCL Psychology subject pool (M_{age} = 20.1 years, *SD* = 2.76, range = 18 to 27, 3 male, 13 right-handed) volunteered to participate in the study in exchange for course credit. They all had normal or corrected to normal vision and no known history of brain disease. The study was approved by the UCL ethics committee (Ref. number: CPB/2014/007).

5.6.2 Materials and Stimuli

The same stimuli as in the previous task were used, with the central face and dot appearing for a random inter-trial interval between 0.5 and 2.5 seconds. When the subject fixated on the dot after the random inter-trial interval, the face and dot either disappeared and one peripheral target appeared until fixated (non-competition condition) or the face and dot disappeared for 0.7sec, without any target appearing until

the next trial started (*Figure 5.17*).

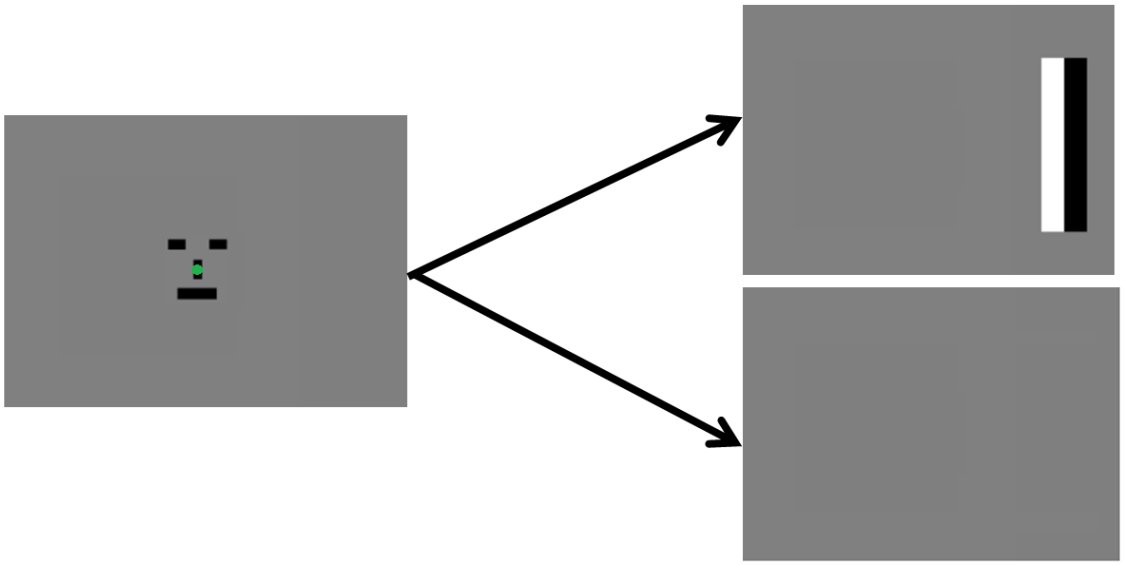


Figure 5.17. Stimulus display used for the offset study. Stimuli used for study 2 are identical to study 1; however, the central face either disappears while a peripheral target appears (non-competition condition) or while no stimuli appear (offset condition).

5.6.3 Procedure

The participant was seated on a chair facing the screen. Subjects were asked to focus on a central green dot and either look at the bars that randomly appeared on either side of the screen or keep fixating on the centre if the face disappeared while no bars appeared. When the central face and dot reappeared, the subjects were asked to shift their focus back to the green dot. Short breaks were given between each set of 100 trials, with a longer break occurring after 200 trials. The entire experiment was composed of 400 trials (200 for the offset condition, 100 for left targets and 100 for right targets, presented in a random order) and lasted for approximately 20 minutes. The same number of offset and target trials were chosen to avoid an oddball effect of the offset condition.

5.6.4 Design

ERP amplitudes and latencies were compared in different steps to investigate the effect of the offset. The offset response was subtracted from the response in non-competition conditions for the subject groups recruited for the current study and subsequently compared with the competition condition of the subject group in the previous study. A 2x2x2 mixed design investigate the effect of condition (non-

competition minus offset or competition), brain hemisphere (ipsilateral or contralateral to the eye movement) and brain side (left or right) on the dependent variables ERP amplitude and latency.

5.7 Results 2

5.7.1 Data processing

On average, 12.7% (SD = 1.64%) of trials were interpolated across all subject based on their individual MAD noise thresholds (see Chapter 2, section 2.3 for details), with all subjects having less than 17.3% interpolated trials. The individual noise threshold for ERP samples was 17.4 µV (*SD* = 7.15 µV), and the amplitude range threshold between minimum and maximum within epochs was on average 64.5 µV (*SD* = 23.16 µV). The average number of trials subjects successfully completed behaviourally was 389 (*SD* = 26.38). After exclusion of noisy EEG data, 353 (*SD* = 31.3) trials remained in the analysis.

In order to investigate the possibility that the differences in peak latencies and amplitudes may be due to an overlap of the offset response to the central target with the onset response of the peripheral stimulus, the offset response data was subtracted from the non-competition condition data and peak latencies and amplitudes for the difference wave were calculated for the same time windows and electrode clusters used in study 1. The following analyses were subsequently performed (only for single target conditions). (1.) A linear mixed model including participants as random effects was used to determine differences between the raw wave and the difference wave (2.) Non-competition condition data from group 1 was compared with the raw non-competition condition data from group 2 to ensure that there were no significant differences between the two sample groups. If groups differed significantly in peak amplitude or peak latency, the differences were accounted for by adjusting peak or latency values of group 2 by adding the difference. (3.) The competition condition of group 1 was compared to the difference between non-competition conditions minus the offset response in group 2 using a linear mixed model including participants as random effects and condition (non-competition minus offset or competition), brain side (left or right) and brain hemisphere (ipsilateral or contralateral) as factors, to investigate which of the effects observed in study 1 are still present after excluding the offset response.

5.7.2 EEG results

Detailed topographical plots of the neural responses in the non-competition condition are displayed in Appendix H. As in the previous study, they show a small contralateral positivity in posterior areas that is followed by a greater posterior positivity that moves to the ipsilateral side and coincides with a frontal negativity (*Figure 5.18*). The similarity to the topographical response pattern in study 1 suggests that responses of subject groups in both studies are comparable. In the following amplitudes will be reported in µV and latencies in ms.

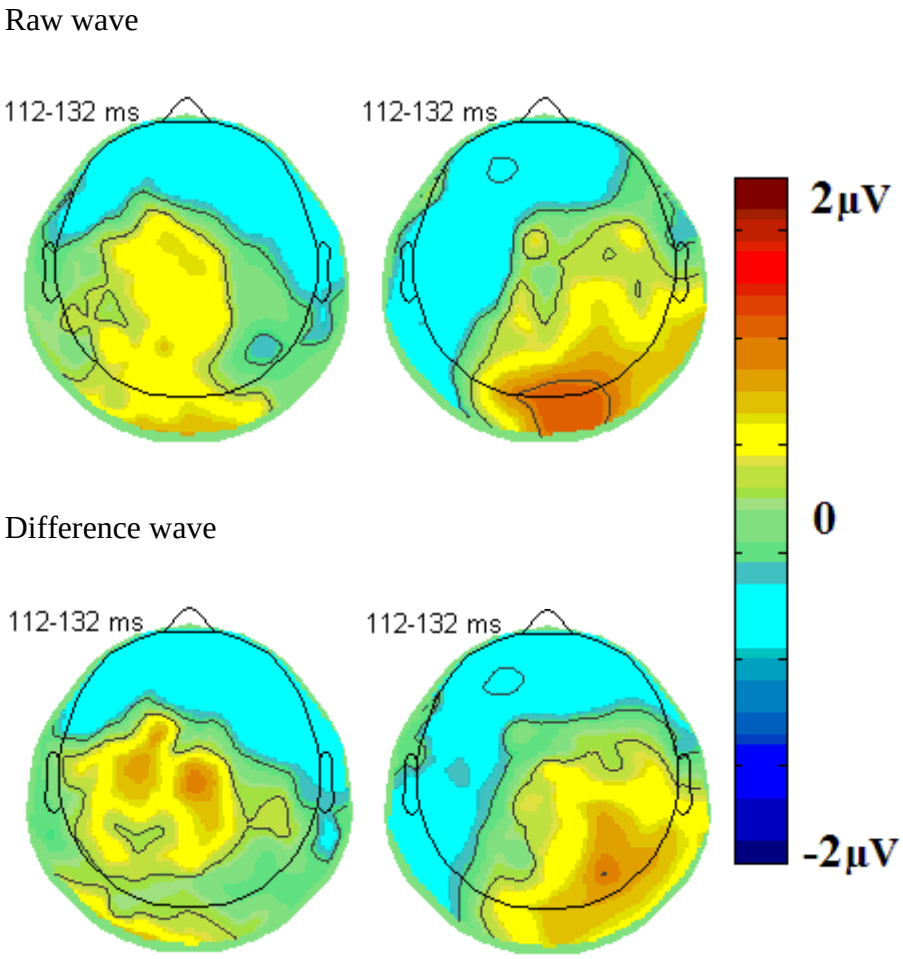


Figure 5.18. Topographical plots of responses in the offset study. Posterior positive response to single targets appearing on the left (left) and right (right) side for the raw wave (top) and after subtraction of the offset response (bottom). Scale: -2µV (blue) to 2µV (red).

Posterior responses

As in the previous study, responses were extracted in two electrode clusters around the occipital electrode locations O1 and O2 (see Chapter 2, Figure 2.4 and section 2.3.2 for details on the extracted electrodes). Wave plots of the raw responses in occipital areas show a similar pattern to the previous study, with a small positivity peaking between 40-90 ms after target onset, followed by a greater peak between 100-180 ms (*Figure 5.19*), suggesting that datasets are similar for both studies. The response in the offset condition showed small positivities around 40-90 and 100-160 ms as well, followed by a negativity peaking towards the end of the extracted time window. The negativity was most pronounced in the offset wave (*Figure 5.20*).

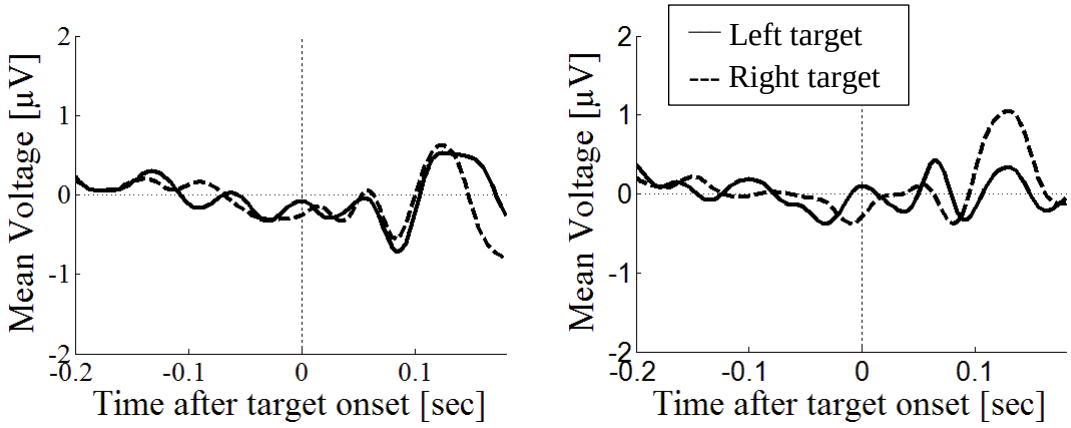


Figure 5.19. Wave plot of the *raw* occipital response in the left hemisphere (left) and the right hemisphere (right) of the brain in the non-competition condition.

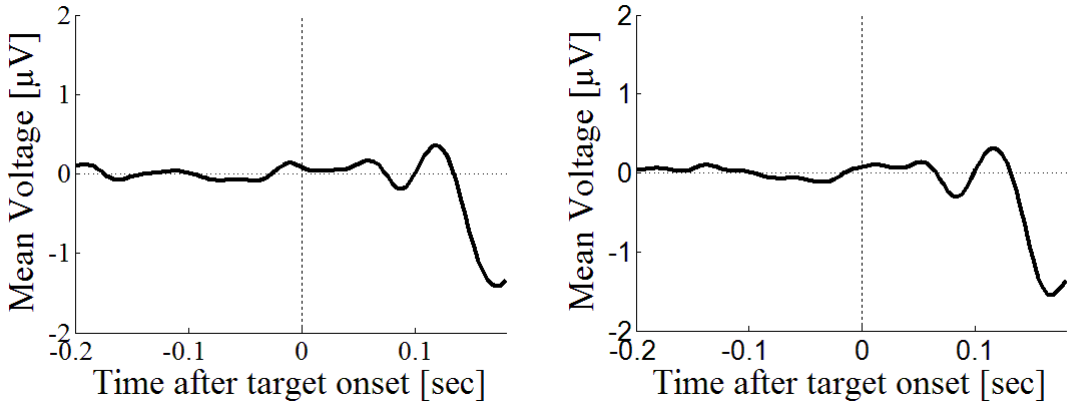


Figure 5.20. Wave plot of the *offset response* in occipital areas in the left (left) and right (right) brain hemisphere.

Early posterior positivity

Difference between raw and difference wave

The early posterior positivity showed no significant differences between raw and difference wave in amplitude, $F(1,97) = 1.99$, $p = .161$ (raw wave: $M = 0.63$, $SD = 0.96$, difference wave: $M = 0.94$, $SD = 1.69$), or latency, $F(1, 97) = 0.23$, $p = .630$ (raw wave: $M = 69.6$, $SD = 17.2$, difference wave: $M = 71.1$, $SD = 17.8$).

Comparison of group 1 and 2

There were no significant differences between group 1 and 2 in peak amplitude, $F(1, 36) = 0.09$, $p = .772$ (group 1: $M = 0.50$, $SD = 2.10$, group 2: $M = 0.63$, $SD = 0.96$), or peak latency, $F(1, 36) = 0.05$, $p = .832$ (group 1: $M = 68.6$, $SD = 19.7$, group 2: $M = 69.6$, $SD = 17.2$).

Comparison of difference wave with competition condition

A comparison of the competition condition of group 1 with the difference wave of non-competition minus offset of group 2 showed no significant effects on peak amplitude, but a significant interaction effect of brain hemisphere and brain side on peak latency, $F(1, 108) = 6.01$, $p = .016$, with shorter ipsilateral latencies in the left and shorter contralateral latencies in the right hemisphere, *Figure 5.21*, replicating the previously observed effect.

In summary, the early posterior positivity was similar in the raw and the difference wave and it confirmed the previously observed interaction effect of brain side and hemisphere on peak latency.

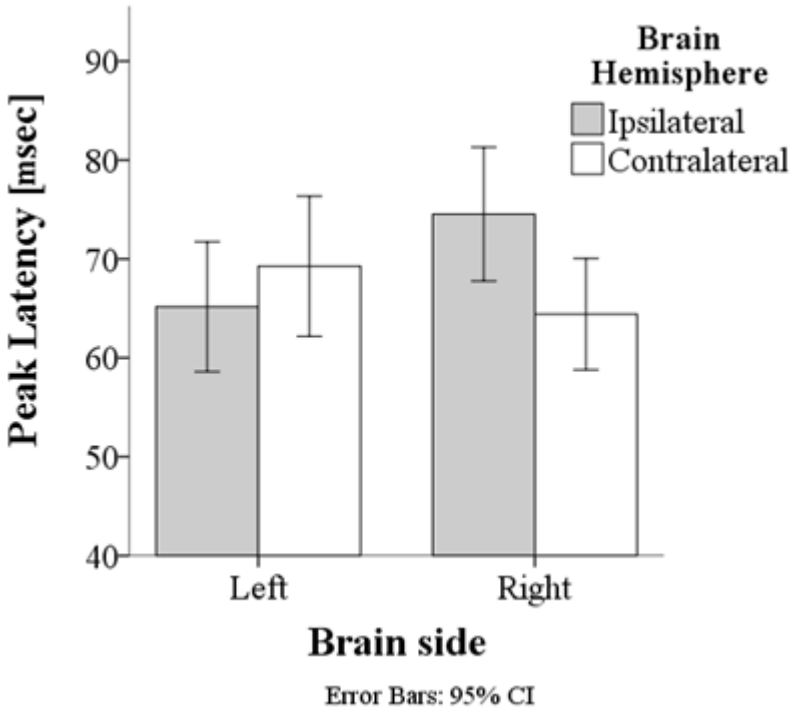


Figure 5.21. Interaction effect of brain side and hemisphere on the early posterior peak latency. Peak latencies (displayed for the extracted time window from 40 to 90 ms after target onset) are shorter in the ipsilateral hemisphere for the left brain side and in the contralateral hemisphere for the right brain side.

Later posterior positivity

Difference between raw and difference wave

The amplitude of the later posterior positivity significantly differed between the raw and the difference wave, $F(1, 97) = 6.49$, $p = .012$, $d = 0.398$, with smaller amplitudes in the raw wave ($M = 1.68$, $SD = 1.60$) than in the difference wave ($M = 2.55$, $SD = 2.63$). Latencies also significantly differed between the raw and the difference wave, $F(1, 97) = 5.24$, $p = .024$, $d = 0.348$, with shorter latencies in the raw wave ($M = 141$, $SD = 26.2$) than in the difference wave ($M = 151$, $SD = 26.7$).

Comparison of group 1 and 2

There were no significant differences between group 1 and 2 in peak amplitude, $F(1, 36) = 0.33$, $p = .569$ (group 1: $M = 1.32$, $SD = 2.91$, group 2: $M = 1.68$, $SD = 1.60$). However, groups differed in peak latency, $F(1, 36) = 8.61$, $p = .006$, $d = 0.652$, with significantly shorter latencies in the first group ($M = 127$, $SD = 18.2$), than in the second

group (M = 141, SD = 26.2), suggesting that no further comparisons of peak latency should be made between groups without correcting for the latency difference.

Comparison of difference wave with competition condition

A comparison of amplitudes in the competition condition of group 1 with the difference wave of non-competition minus offset of group 2 showed a significant effect of condition, $F(1, 108) = 4.42$, $p = .043$, $d = 0.577$, on peak amplitude, with greater amplitudes in the non-competition condition (M = 2.55, SD = 2.63) than in the competition condition (M = 1.17, SD = 2.11), which is comparable to the previously observed effect that was previously only significant in the double target condition. In addition there was a marginal effect of brain hemisphere, $F(1, 108) = 3.01$, $p = .085$, $d = 0.191$, with greater amplitudes in the ipsilateral (M = 1.91, SD = 2.40) than in the contralateral hemisphere (M = 1.45, SD = 2.39).

Group differences in peak latency were adjusted by subtracting the 14.7 ms difference in peak latency between groups from the values in the second sample group. After this correction, a comparison of the competition condition of group 1 and the difference wave of group 2 showed only a significant interaction effect of brain hemisphere and brain side, $F(1, 108) = 6.14$, $p = .015$, showing longer ipsilateral latencies in the left than in the right brain side, similar to the previously observed effects (*Figure 5.22*). The difference between non-competition minus offset (M = 151, SD = 26.7) and competition conditions (M = 157, SD = 24.4) was no longer significant, $F(1, 36) = 1.69$, $p = .201$, $d = 0.262$, *Figure 5.23*.

In summary, raw and difference wave of the late occipital positivity differed significantly, with smaller amplitudes and shorter latencies in the raw wave than in the difference wave. Peak amplitudes were greater in the non-competition than in the competition condition and slightly greater in the ipsilateral than in the contralateral hemisphere. The interaction effect of brain side and hemisphere on peak latency was confirmed.

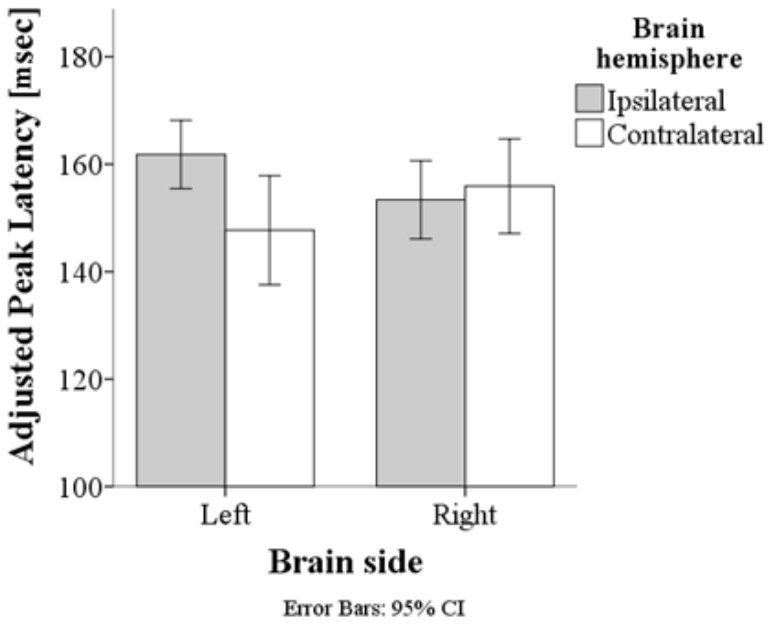


Figure 5.22. Interaction effect of brain side and hemisphere on the later occipital peak latency. The adjusted peak latencies are longer in the ipsilateral hemisphere for left than for right targets.

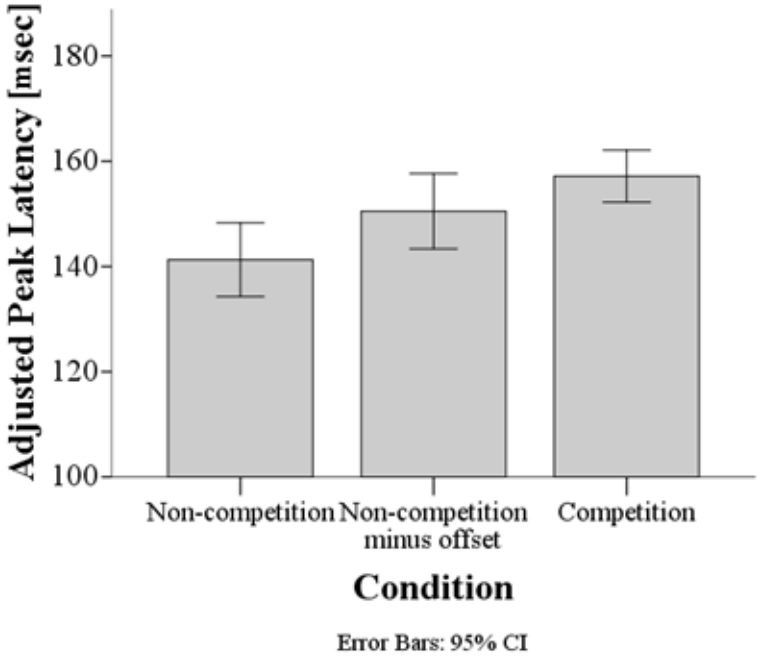


Figure 5.23. Occipital peak latencies adjusted for the difference between the two subject groups. Latencies are shortest in the non-competition condition, intermediate in the difference wave of non-competition minus the offset response and longest in the competition condition.

Frontal responses

As in the previous study, frontal responses were extracted in two lateral fronto-central electrode clusters (see Chapter 2, Figure 2.5 and section 2.3.2 for details on the extracted electrodes). Frontal areas showed a negative response between 100 and 180 ms that was comparable to the response observed in the previous study. It was preceded by a small contralateral positivity (*Figure 5.24*). The offset response also showed an early small positivity (*Figure 5.25*); however, the negativity was less pronounced and directly followed by a greater positivity.

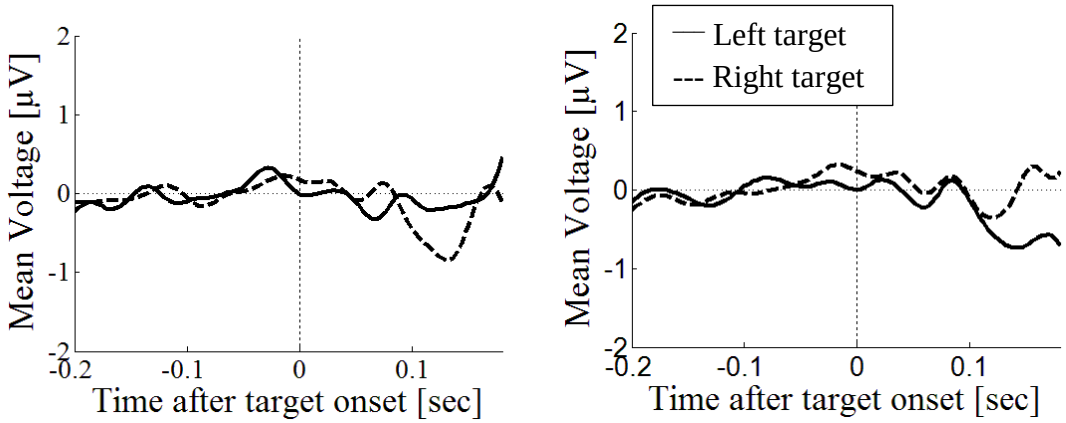


Figure 5.24. Wave plot of the *raw* frontal response in the left hemisphere (left) and the right hemisphere (right) of the brain in the non-competition condition.

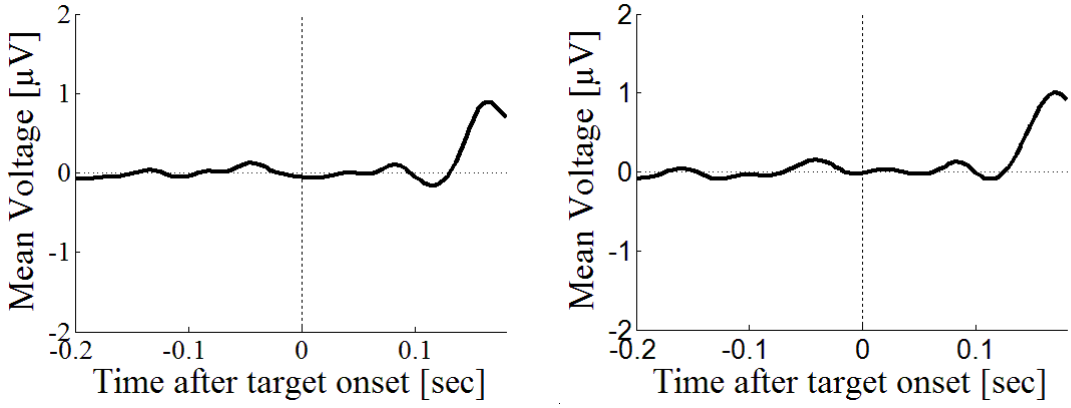


Figure 5.25. Wave plot of the *offset response* in frontal areas in the left (left) and right (right) brain hemisphere.

Frontal negativity

Difference between raw and difference wave

For the frontal negativity there were no amplitude differences between the raw wave (M = -0.93, SD = 3.14) and the difference wave (M = -0.99, SD = 3.87), $F(1, 97)$ = 0.01, p = .917, but a significant difference in peak latency, $F(1, 97)$ = 5.79, p = .018, d = 0.393, with significantly shorter latencies in the raw wave (M = 141, SD = 30.0) than in the difference wave (M = 152, SD = 29.0).

Comparison of group 1 and 2

There were no significant differences between group 1 and 2 in peak amplitude, $F(1, 150)$ = 0.001, p = .972 (group 1: M = -0.96, SD = 6.50, group 2: M = -0.93, SD = 3.41), and only marginal differences in peak latency, $F(1, 36)$ = 3.79, p = .059, with shorter latencies in the first sample group (M = 129, SD = 24.9) than in the second group (M = 140, SD = 30.4).

Comparison of difference wave with competition condition

A comparison of the competition condition of group 1 with the difference wave of non-competition minus offset of group 2 showed no significant effects on peak amplitude.

Group differences in peak latency were adjusted by subtracting the 11.9 ms difference in peak latency between groups from the values in the second sample group. After this correction, a comparison of the competition condition of group 1 and the difference wave of group 2 showed a marginal effect of hemisphere, $F(1, 108)$ = 3.33, p = .071, d = 0.305, with shorter latencies in the ipsilateral (M = 138, SD = 26.5) than in the contralateral hemisphere (M = 146, SD = 24.6) like previously observed in study 1. There was a marginal interaction of condition and brain side, $F(1, 108)$ = 3.83, p = .053, showing longer latencies in the competition condition (as previously observed) than in the difference wave for the left side of the brain but not for the right side (*Figure 5.26*).

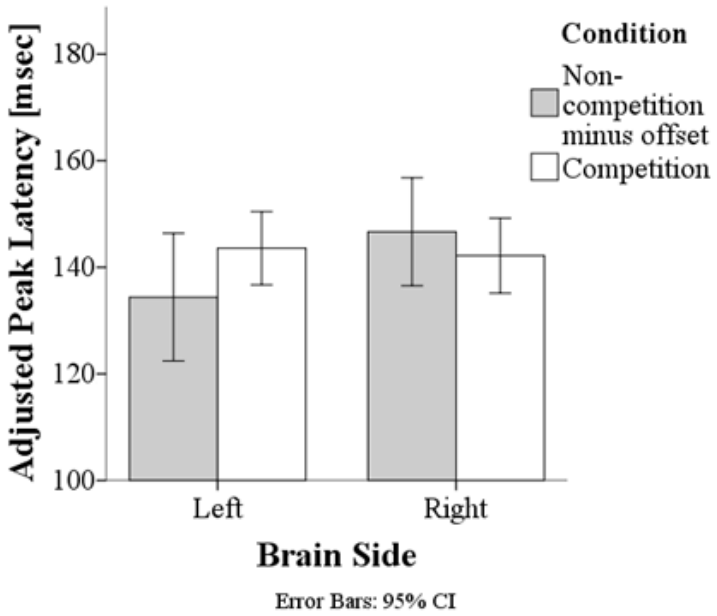


Figure 5.26. Interaction effect of brain side and condition on the frontal peak latency. Adjusted peak latencies are longer in the competition condition than in the non-competition condition in the left side of the brain but not in the right side.

In summary, the frontal negativity had significantly shorter latencies in the raw wave than in the difference wave. The response peaked slightly earlier in the ipsilateral than in the contralateral hemisphere. Latencies under competition were slightly longer than under non-competition but only in the left brain side.

5.8 Overall discussion

The aim of the second study was to identify whether differences between non-competition and competition conditions are the result of a visual response to the offset of the centrally fixated target, by subtracting the offset response from the wave under non-competition conditions. Raw and difference waves differed significantly for the late posterior positivity and the frontal negativity but not for the early posterior positivity.

5.8.1 Early posterior positivity

Although the offset response showed a small early posterior peak, it did not lead to significant differences between the raw and the difference wave in amplitude or latency. The same interaction effect of brain hemisphere and brain side on peak latencies was replicated as was found in study 1, suggesting that the offset only has a negligible effect on the early posterior response.

5.8.2 Later posterior positivity

The later posterior positivity had significantly greater amplitudes and longer latencies when the offset response was subtracted from the raw wave, suggesting that the response is significantly affected by an overlap with an additional response to the offset of the central stimulus.

After subtracting the offset response from the non-competition response, response amplitudes were significantly greater in the non-competition condition than in the competition condition, which has also been found for double targets in the previous study. This is in line with previous research (e.g. Keitel et al., 2013; Moran & Desimone, 1985) suggesting that response amplitudes towards single stimuli decrease the more stimuli are present. Interestingly, the difference between conditions was not significant for single targets in the previous study. The fact that the effect of condition becomes significant for single targets when the offset response is subtracted suggests that the offset of a visual stimulus adds to the scalp potentials, possibly masking the effect. Wave plots of the offset response (*Figure 5.20*) show a posterior negativity towards the end of the extracted window. This negativity overlaps with the occipital positivity measured in the raw wave, resulting in overall smaller amplitudes. A possible explanation is therefore, that in the previous study the effect of condition on peak amplitude was only found for double targets, because the overall amplitude decreases the more stimuli are present, leading to more visible amplitude differences when two targets are present. This is in line with previous studies showing that the effect that attention has on neural responses increases with the number of targets that are presented (Luck et al., 1997). The current study shows that there still is an effect of condition for single targets; however, it is overshadowed by the offset response that adds on to it. Alternatively, as discussed in the previous chapter, the posterior negativity may play a crucial role in ensuring that saccades are inhibited by keeping SC activation from reaching a threshold. In the offset condition, subjects were instructed to keep fixating on the centre of the screen. Hence, the overlap of a response involved in saccade inhibition with target-linked responses may have impacted the observed response pattern.

After subtracting the offset response from the non-competition response, the latencies were still shorter than in the competition condition; however, this effect was no longer significant, suggesting that the visual offset response can account for most of the latency difference between conditions, but that this may be partially due to

additional mechanisms. According to developmental models, visual areas play a crucial role for attention shifts (e.g. Atkinson, 1984; Atkinson, 2000b; M. H. Johnson, 1990, 2002). As discussed in the previous chapter, visual cortical areas can activate SC (Collins et al., 2005; Schiller & Tehovnik, 2005), which in turn generates saccades (Goldberg & Wurtz, 1972a; Schiller & Stryker, 1972) after a specific activation threshold is reached (Neggers et al., 2005). In particular, fMRI studies using the gap paradigm show that the offset of a visual stimulus can activate SC (Neggers et al., 2005). The current results show that the offset of a visual stimulus increases activation in visual areas of the cortex. In line with previous research (Collins et al., 2005; Schiller & Tehovnik, 2005), this activation may lead to higher SC activation, which may be a possible cause of faster attention shifts on non-competition conditions. In a sense, the offset of a visual stimulus 'prompts' the brain to shift attention to another location. This mechanism is beneficial in everyday life, as it is crucial for humans to focus on new things instead of staring at blank locations where once a stimulus was present.

MRI research in human adults has shown that activity in the visual cortex increases when attention is directed towards an area, even without visual stimuli being present (Kastner, Pinsk, De Weerd, Desimone, & Ungerleider, 1999). These attentional processes may be the reason why latencies were still slightly shorter in the difference wave than in the competition condition, as attention is directed later because the additional disengagement process is required.

Results for the posterior response should be treated with caution, because there were group differences in peak latency of this response between the first and second sample group, suggesting that differences might be due to subject differences. This problem was avoided by subtracting the latency difference between groups in the non-competition condition to get them to a similar level. However, the underlying component might differ between subjects; therefore an alternative explanation for the observed effects may be general group differences.

5.8.3 Frontal negativity

The offset response did not affect the amplitude of the frontal negativity; however, peak latencies were significantly shorter for the raw wave than for the difference wave, suggesting that the offset induced an earlier peak. The offset response

wave shows a positivity towards the end of the extracted time window. An overlap of this positivity with the response may result in an earlier peak.

When comparing the non-competition difference wave with the competition condition the latency differences between non-competition conditions and competition conditions that were previously found in study 1 were no longer significant. The frontal negativity is therefore significantly related to the offset of a target. An interaction of condition and brain side showed that the latency difference was still present in the left side of the brain but not in the right side. The patterns of effects on the frontal negativity were similar to those observed for the occipital positivity, suggesting that they may be part of the same dipole.

5.8.4 Further responses

The offset wave showed a small positivity in frontal areas, peaking between 80 and 100 ms post target. A similar small positivity was observed in the raw wave in study 1 in non-competition conditions and in the contralateral hemisphere only. Csibra et al. (1997) observed a similar prefrontal positivity in gap trials and related it to the offset of the central fixation stimulus. The experiments in this chapter provide further evidence for this early frontal peak being related to the stimulus offset, as it could also be observed in the offset wave.

5.8.5 Systems underlying attention mechanisms

Non-competition and competition conditions generally showed similar responses. There may be a lack of differences between conditions because disengagement is required in both conditions (i.e. disengagement from the spatial location), but the disengagement is easier without a central stimulus being present. Alternatively, differences in higher-order processing areas may occur at a later time (e.g. linked to saccades as investigated in previous studies (e.g. Csibra et al., 1997; Kawakubo et al., 2007; Moster & Philadethia, 1991)), which could not be investigated because of potential overlaps with saccades. Another explanation would be that specific activity related to disengagement may take place in deep brain structures that cannot be picked up using EEG, for example neurodevelopmental models suggest the subcortical substantia nigra to be an additional source of collicular inhibition (Atkinson, 2000a; M.

H. Johnson, 1990; Schiller, 1985). Additional MRI studies could provide further insights into deep brain responses during attention shifts.

Despite the similarity of the main responses, response latencies already differed at an early processing level, especially in occipital areas. Different models have suggested the occipital cortex to play a crucial role for overt attention shifts (Atkinson, 1984; M. H. Johnson, 1990; Schiller, 1985). The current study confirms that occipital responses reflect the latency pattern that is also found for saccades and differ significantly between competition and non-competition conditions. It furthermore suggests that the offset of visual stimuli may play a crucial role in preparing the brain to shift attention. The offset response could account for the majority of differences between conditions, but not all of them, suggesting that occipital areas interact with additional input pathways from other areas, as suggested by previous models (e.g. Atkinson, 1984; Atkinson, 2000b; M. H. Johnson, 1990, 2002).

Schiller (1985) proposed different systems to be involved in attention shifts, depending on the task difficulty, involving visual cortex for simple shifts and FEF for shifts that involve additional processing. This study shows that a posterior system is influenced by visual input that redirects the eyes when visual input disappears. The visually dependent system may be responding faster, leading to faster saccades in non-competition conditions. Adults' ability to shift attention is well developed, and the FSP may be too simple to activate additional systems involved in more complex processing. The double target condition introduces an extra difficulty. Topographical plots of the response showed a later positivity in frontal areas for double target conditions only. This response may reflect higher processing mechanisms becoming active.

Hood and Atkinson (1993) suggested that shorter saccadic latencies in non-competition conditions than in competition conditions may either be due to the gap or target offset priming the system to make a response in non-competition conditions or due to additional disengagement processes prolonging latencies in the competition condition. The current study shows that when the offset response is subtracted from the non-competition response, occipital ERP latencies become significantly longer, suggesting that the latency difference is partially caused by the offset which may prime the system to shift attention, while disengagement may play a smaller role in attention shifts. The current study measured scalp potentials, making it difficult to investigate whether the stimulus offset has a direct effect on attention shifts or whether the offset

response simply adds on to the measured scalp response. Additional neuroimaging techniques may provide further insights about the location of the offset response and principal component analyses may provide details on separate neural sources of offset-related and target-related responses and will be discussed in Chapter 7 (section 7.2.4).

5.8.6 Summary and conclusion

This chapter investigated neural mechanisms of attention shifts with and without competing targets in adults. It replicates behavioural findings of previous research, showing shorter saccadic latencies in non-competition conditions that in competition conditions. These latency differences were also found on an early neural level in occipital areas of the brain, suggesting that early cortical mechanisms may be involved in attention shifts. The studies confirm a crucial involvement of occipital areas in attention shifts, as suggested by neural models of attention, while frontal areas were more involved in saccade inhibition (frontal negativity) and more complex tasks involving multiple stimuli (frontal positivity). Separate analyses of the offset response suggest that occipital responses are affected by the visual offset in non-competition conditions, explaining the majority of differences between attention shifts in competition and non-competition conditions. The next chapter investigates how brain mechanisms of attention shifts develop during infancy.

Chapter 6 The developmental of neural mechanisms of attention during infancy

6.1 Introduction

The previous chapter investigated brain mechanisms of overt attention in adults and showed that occipital and fronto-central response latencies already differ between non-competition and competition conditions within 180 ms after target onset. The current chapter aimed to investigate how brain mechanisms of attention develop with age by using the same methods to test infants in the first year of life. Performance in the FSP improves with age (see Chapter 1, section 1.3), which was confirmed using eye-tracking in Chapter 3. The first part of this chapter investigated the development of brain responses under non-competition and competition conditions. The second section studied how these responses differ when infants get stuck on the central stimulus compared to when they successfully re-fixate.

6.1.1 Previous findings on ERPs during attention shifts in infants

Neural mechanisms of attention shifts have been studied extensively in adults, as they can simply be instructed to covertly shift their attention, allowing for clean EEG data free of eye movement artefacts. Covert shifts induced by a cue before an overt shift have furthermore been investigated in infants between 3 and 6 months of age (e.g. Richards, 2000; review: Richards, 2004; Richards, 2005). Similar to adults (e.g. Harter et al., 1982; Heinze et al., 1990; Luck et al., 1990; Mangun, 1995; Rugg et al., 1987), infants show larger occipital response amplitudes towards attended compared to unattended stimuli (Richards, 2000, 2005). They furthermore show a central negativity related to attention (de Haan, 2007b; Richards, 2003a).

Overt attention shifts in infants have widely been studied on a behavioural, but rarely on a neural level (see: Csibra et al., 1998; Csibra et al., 2000). Csibra et al. (1998) investigated neural mechanisms of attention shifts in the gap paradigm with EEG. They only tested 6 months old infants, who according to previous research (e.g. Hood & Atkinson, 1993), already have a fairly well developed ability to shift attention and rarely show sticky fixations; however, their saccade latencies under competition were still delayed (Csibra et al., 1998). Csibra et al. (1998) found the typical behavioural differences in saccade latencies between gap and overlap trials. On a neural level, target locked ERPs in occipital areas showed a negative-positive-negative response pattern

within the first 200 ms after target onset that did not significantly differ between conditions. However, frontal areas showed a left-lateralised positivity that significantly differed between conditions, being greater in gap than in overlap conditions between 80 and 200 ms post stimulus in central and between 20 and 200 ms in left-lateral areas (Table 6.1). Csibra et al. (1998) suggest that this frontal effect may reflect disinhibition of the superior colliculus (SC) through frontal eye fields. Saccade-linked responses that are typical in adults, including a spike potential directly preceding the saccade, were not observed in 6 months old infants (Csibra et al., 1998) but emerged at 12 months of age (Csibra et al., 2000).

Table 6.1. *Summary of target-locked ERPs observed in infants by Csibra et al. (1998) in the gap paradigm.*

Response	**Timing**	**Variation between conditions**
Occipital negative-positive-negative response pattern	Within 200 ms	No differences between conditions
Frontal left-lateralised positivity	80 to 200 ms	Greater amplitudes in gap than in overlap conditions

Csibra et al. (1998) only explored brain responses in gap and overlap conditions, while a non-competition condition, with immediate appearance in the periphery when the central target disappeared, was not used in their paradigm. The gap condition shows a different time course of responses, as a disengagement from the centre is possible before a peripheral target appears. This may lead to more temporally expanded neural responses. In the non-competition condition the peripheral target appears simultaneously with the disappearance of the central stimulus, making the time-course more comparable to the competition/ overlap condition. This study therefore aimed at comparing neural responses in competition and non-competition conditions. Furthermore, M. H. Johnson (1990) suggests that all major attention shift pathways have already developed at an age of 6 months and the greatest changes in saccade latency during attention shifts occur before 3 months of age (Atkinson, 1984, 2000a; Hood & Atkinson, 1993). Therefore, younger infants were tested in this study, starting at an age of 1.5 months, which is before major improvements in saccade latency and sticky fixations occur, allowing an investigation of differences between young infants

and older infants who have an improved ability to shift attention. In particular, sticky fixations rarely occurred in the age group tested by Csibra et al. (1998), and could therefore not be investigated further. In the age group tested for this study, sticky fixations are more common and therefore, brain responses during sticky fixations could be explored.

Other saccade-related potentials involve an anterior positivity preceding saccades by 50 ms (e.g. Richards, 2005). This response only evolves after 20 weeks of age and should therefore only be visible in the oldest age group tested for this study. Further responses that have been related to attention occur late after target onset, for example the negative central component between 600 and 1200 ms after target onset (Karrer & Monti, 1995; Nelson, 1997; Webb, Long, & Nelson, 2005) and later slow waves (e.g. K. Snyder, Webb, & Nelson, 2002; Webb et al., 2005), see Chapter 2, section 2.2.3 for details. These responses would overlap with saccades and can therefore not be further investigated in this study.

In summary, attention shifts in young infants have been found to involve occipital responses (Csibra et al., 1998; Richards, 2000, 2005) and a frontal positivity (Csibra et al., 1998), possibly reflecting attentional control by frontal eye fields.

6.1.2 Predictions derived from neurodevelopmental models

ERPs in infants

Changes in ERP features during infancy are discussed in Chapter 2, section 2.3.3 and prompt the following predictions for the current chapter.

1. As peak amplitudes increase until 6 months of age and decrease from then onwards (Barnet et al., 1980; Hou et al., 2003; Sokol & Dobson, 1976), there should be an increase in amplitude from the youngest infant group tested in this study (1.5-2.5 months) to the oldest group (5.5-7.5 months).
2. As the number of distinct components that can be distinguished in wave forms increases with age (Barnet et al., 1980; Nelson & Luciana, 1998), older infants should show more distinct components than younger infants.

To facilitate the comparison of infant and adult responses despite numerous differences, the same task and stimuli were used for both groups in this thesis.

Theories of brain development

Different neurodevelopmental models of attention have been reviewed in Chapter 1, and can prompt the following predictions about cortical responses during attention shifts in the current study:

1. Cortical involvement should increase with age (Atkinson, 1984, 2000a; Braddick et al., 1992; Bronson, 1974) with subcortical SC pathways and inhibitory pathways active before 1 month, leading to infants becoming stuck on visual stimuli. Both of these processes are mainly subcortical; therefore, only small cortical responses should be observable with EEG at this age. After 1 month cortical control starts emerging (Atkinson, 1984; Bronson, 1974; M. H. Johnson, 1990), suggesting that all infants tested in this study (1.5-7.5 months) should show some form of cortical responses.
2. Between 1 and 2 months an excitatory pathway from visual areas to SC becomes active, leading to the SC saccade execution threshold being reached earlier. This should result in posterior responses that can be detected with EEG.
3. Between 3 and 6 months the FEF allows more controlled shifts (Atkinson, 1984, 2000a; M. H. Johnson, 2002). This suggests that anterior areas should increasingly become involved in attention shifts in infants between 3 and 6 months.
4. Interhemispheric connections play a crucial role in the development of attention shifts (Bartolomeo et al., 2007; De Schotten et al., 2005; Elison et al., 2013). Therefore, the lateralisation of ERPs may also have important effects on attention shifts.

In summary, cortical responses should become visible around 2 months of age, mainly involving posterior activation, while frontal responses increasingly become active between 3 and 6 months.

6.1.3 Aims and hypotheses

This experiment aimed at investigating the development of neural mechanisms of attention shifts during infancy using the task that was developed throughout this thesis. In line with previous research and findings in Chapter 3, it was expected that saccade latencies and the proportion of sticky fixations in competition conditions

decrease with age. For the double target condition, longer latencies were expected than for single target conditions, as described in Chapters 4 and 5.

In line with early neurodevelopmental models (Atkinson, 1984; Bronson, 1974; M. H. Johnson, 1990), it is predicted that cortical responses become increasingly involved in attention shifts with age. In particular, frontal areas were expected to become more involved between 3 and 6 months. Together with findings from Csibra et al. (1998), posterior areas are expected to show a pattern of negative-positive-negative responses, while a positivity was expected to occur in frontal areas, which, in line with neurodevelopmental models, should increase in amplitude with age. The factor brain side (left or right) was included in the analysis to investigate whether the frontal response is left lateralised as suggested by Csibra et al. (1998) or right lateralised as suggested by adult attention models (Corbetta & Shulman, 2002, 2011). As sticky fixations reflect a failure of neural mechanisms to initiate a saccade, different response patterns were expected for sticky fixations, involving less anterior activity from frontal eye-fields related to less attentional control.

6.2 Method

6.2.1 Participants

Seventy-one infants (Mean age = 4.00 months, *SD* = 2.01, range = 1.45 to 7.85, 38 female) were recruited from the Visual Development Unit's database. Nine additional infants were excluded from the analysis because they were asleep or because they did not tolerate the EEG cap. Infants were split into 4 groups: 1.5-2.5 months (*n* = 22, *M* = 2.03, *SD* = 0.24, range = 1.45 to 2.41, 12 female), 2.5-3.5 months (*n* = 20, *M* = 3.05, *SD* = 0.32, range = 2.57 to 3.49, 14 female), 3.5-5.5 months (*n* = 12, *M* = 4.55, *SD* = 0.46, range = 3.79 to 5.54, 5 female) and 5.5-7.5 months (*n* = 17, *M* = 6.76, *SD* = 1.01, range = 5.57 to 7.85, 7 female). This age split allows an investigation of different developmental steps suggested by previous models (Atkinson, 2000a; M. H. Johnson, 1990), while avoiding excessive variations within groups, as previous research suggests that infants within a groups should not differ in age by more than 2 months (e.g. DeBoer et al., 2007; Picton et al., 2000). Parents volunteered to participate with their infants in return for reimbursement of travel expenses. Infants were all born within 14 days of term and had no known history of neurological problems. The study was approved by the UCL research ethics committee (Ref. number: 2002/02) and by the NHS (REC Ref. 14/LO/0610).

To increase data quality, strict criteria were applied for subject exclusion, only including infants who correctly responded to the target (no sticky fixations, or responses to the wrong direction), without data loss from either eye-tracker or EEG (as determined by the algorithms described in Chapter 2, section 2.2.3 and 2.3) in at least 5 trials for every condition, leaving 29 infants in the final analyses that were split into four age groups (see Table 6.2 for details). This high attrition rate is common in infant research (e.g. Csibra et al., 1998; Csibra et al., 2000; de Haan & Nelson, 1997). The analyses reported in this chapter only include data from infants who met these strict criteria. However, analyses including all infants can be found in Appendix I (behavioural analyses) and Appendix L (EEG analyses). A linear mixed model showed no significant differences in saccade latency between the included (M = 0.630, SD = 0.589) and excluded infants (M = 0.731, SD = 0.807), $F(1, 60) = 2.75$, $p = .102$ and no interaction with age group, $F(3, 56) = 1.00$, $p = .402$. A mixed logistic regression showed no significant difference in the percentage of sticky fixations between included (2.1%, SD = 14.3%) and excluded (4.4%, SD = 21.0%) infants, $z = -1.59$, $p = .111$, and no interaction of inclusion criteria with age, $z = 1.10$, $p = .271$, suggesting that both groups of infants are behaviourally comparable.

Table 6.2. *Number of infants within the different age groups and demographic details (mean age and standard deviations).*

Age group	N	Mean age	SD	Age range	Gender ratio (male : female)
1.5-2.5 months	10	2.03	0.23	1.58 – 2.37	4:6
2.5-3.5 months	7	2.91	0.26	2.60 – 3.46	4:3
3.5-5.5 months	6	4.36	0.40	3.79 – 5.08	4:2
5.5-7.5 months	6	6.32	0.61	5.53 – 7.19	4:2

6.2.2 Materials and Stimuli

Each trial began with a cartoon being presented on the computer screen for at least 3.3 sec (200 frames) to attract the infant's attention. If, during this time interval, the experimenter had indicated by pressing a button that the infant was alert and if the infant fixated on the cartoon, i.e. fixated less than 8.8 degree of visual angle from the

centre of the screen for at least 330 ms, the movie disappeared, while sounds where still audible and the first stimulus, a high contrast schematic face, that changed "expression" at a rate of 3 Hz, subtending a visual angle of 7.7° x 7.7° appeared. From then on trials were comparable to the adult FSP study. The central face remained visible for a randomised inter-trial interval between 0.5 and 2.5 seconds before the target occurred. When the subject fixated on the face after the random inter-trial interval, target stimuli were randomly presented on the left, right or on both sides of the screen at an eccentricity of 12.9° of visual angle. Target stimuli were bars made up of one black and one white rectangle that reversed colour at a rate of 3 Hz. In competition conditions the central face remained on the screen whereas in the non-competition condition, it disappeared at the onset of the bars (*Figure 6.1*). All conditions (number of bars, screen side and competition vs. non-competition) were presented in a random order.

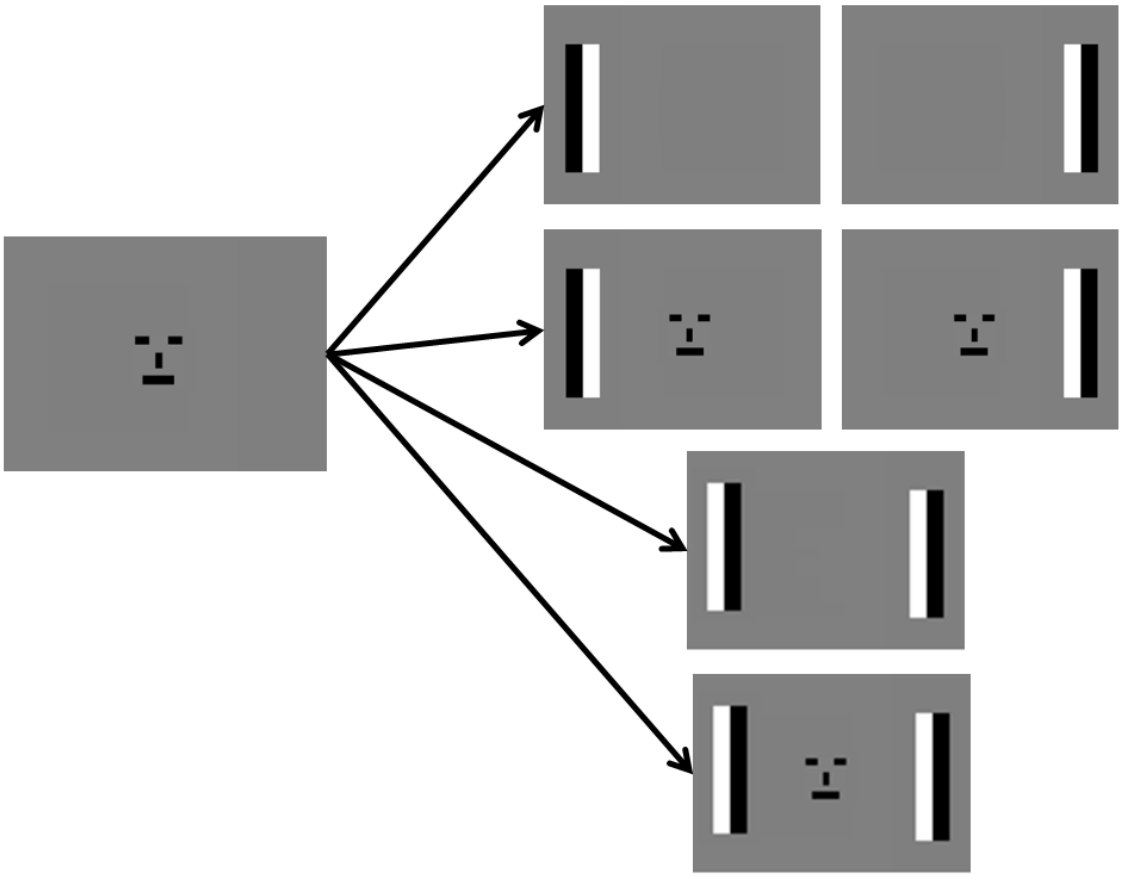


Figure 6.1. Target displays in different conditions. Target displays in single target (top) and double target (bottom) conditions and with competition (central face visible) and non-competition (central face disappears) conditions.

6.2.3 Procedure

Before the participants arrived, the eye-tracker was calibrated on an adult using a standard five point routine to ensure a proper completion of the calibration (see Chapter 2, section 2.2.2 for details). When the infant arrived, the EEG caps were prepared and adjusted. After babies became familiar with the lab environment they were seated on their parent's or caregiver's lap facing a screen. Parents or caregivers wore sunglasses to prevent eye movement recording and were instructed to keep as still as possible to avoid motion artefacts. Additionally, the experimenter could pause trial onsets manually when infants were moving or getting fussy.

Before the main experiment began, a brief calibration was run. The infant watched a cartoon on the screen, while it was monitored whether the eye-tracker received a signal. If necessary for the individual infant, lights in the room were adjusted, the position of the infant was changed and neutral density filter were placed in front of the eye-tracker to improve signal strength (details on data quality improvements in Chapter 2, section 2.2.2, discussion: Chapter 7, section 7.2.2).

After the ideal eye-tracking signal was established, lighting conditions were kept constant and the experimentation programme was started. Infants watched a cartoon and if the experimenter judged them as being alert and they were fixating on the screen, a trial automatically began with the presentation of the central face stimulus. If the infant kept fixating on the screen, target stimuli appeared on either side of the screen. If the infant looked at these targets, they disappeared and the video reappeared. If the infant got "stuck" on the central face for longer than 5 seconds (10 seconds for infants under 4 months), the face disappeared and the cartoon reappeared.

Short breaks were given between trials, when the infant became inattentive or started crying. The experiment ended when the infant got tired or restless, which happened on average after 56.17 trials (*SD* = 23.28, *min* = 14, *max* = 118)[4].

6.2.4 Design

In a mixed design the effect of the within-subject factors, competition condition (competition or non-competition), screen side watched (left or right) and the number of

[4] The Smaller groups of infants included in the final data analysis completed on average 74.54 trials (*SD* = 18.50, *min* = 46, *max* = 116).

peripheral targets (one or two) and the between-subjects factor age group (1.5-2.5, 2.5-3.5, 3.5-5.5 and 5.5-7.5 months), on the dependent variables saccade latency and the effect of the within-subject factors competition condition (competition or non-competition), hemisphere (ipsi- or contralateral to the eye movement), brain side (left or right) and the between-subjects factor age group (1.5-2.5, 2.5-3.5, 3.5-5.5 and 5.5-7.5 months) on ERP amplitude was investigated. As in the adult studies, two measures of brain lateralisation were taken: *brain hemisphere* describes the lateralisation in relation to the target (hemisphere ipsi- or contralateral to the stimulus that was reacted to) and the factor *brain side* compares the left and right side of the brain.

6.3 Results

6.3.1 Data processing

The methodology chapter describes the method used for pre-processing eye-tracking and EEG data used throughout this thesis (see Chapter 2, section 2.2.3 and 2.3). Mixed linear models were calculated in SPSS (IBM Corp, 2011) to investigate saccade latencies and ERP amplitudes, while mixed effect logistic regressions were calculated in R (Core Team, 2012) through RStudio, Version 0.97.551, to investigate effects on binary outcome variables (e.g. sticky fixations).

EEG data was pre-processed as described in Chapter 2 (section 2.3). On average, 10.9% (SD = 3.4%) of epochs were interpolated across all subject, with all subjects having less than 22.5% interpolated epochs. The individually calculated noise threshold for ERP data was on average 39.4 µV (*SD* = 20.2 µV), and the amplitude range threshold between minimum and maximum within epochs was on average 139 µV (*SD* = 73.1 µV). After exclusion of noisy EEG data, an average of 63.4 (*SD* = 19.9) trials per subject remained in the analysis[5]. Table 6.3 displays the average and SD of successful trials of the infants included in the analysis by conditions and age group.

[5] The greater group of infants, part of whom got excluded from the analysis had 10.9% of trials interpolated (*SD* = 3.49, *Max* = 22.5), an average noise threshold of 39.5 µV (*SD* = 20.3), range threshold of 139 µV (*SD* = 68.3) and on average 47.7 (*SD* = 22.1) trials remained in the analysis. Included and excluded infants only differed in the number of successful trials, t (71) = -5.82, $p < .001$.

Table 6.3. *Average (and SD) of successful trials per condition and age group.*

		1.5-2.5 mo	2.5-3.5 mo	3.5-5.5 mo	5.5-7.5 mo
Non-competition	Left	11.5 (3.72)	10.3 (1.89)	8.5 (2.22)	10.2 (4.01)
	Right	11.1 (3.33)	11.3 (3.82)	11.0 (2.89)	9.3 (2.49)
Competition	Left	10.6 (3.01)	11.3 (1.89)	9.3 (3.35)	10.3 (2.89)
	Right	9.8 (3.46)	10.7 (2.63)	10.3 (2.81)	11.0 (4.83)

6.3.2 Behavioural results

Data quality

Only data from infants who reached the strict criteria for data inclusion in EEG analyses (section 6.2.1) were included in the analysis reported here. However, the findings are similar when all infants are included in the analysis (see Appendix I for the full analysis including all infants). 83.6% of trials were correct re-fixations, 2.0% were sticky fixations, 5.7% of saccades went to the wrong direction, 3.4% were wrong but subsequently corrected and 8.6% of trials were noisy data.

Sticky fixations

Mixed logistic regressions including participants as random effect and condition, age group, number of stimuli and their interactions as fixed factors showed no significant differences in noisy data between conditions. Sticky fixations showed a significant effect of condition, $z = 3.09$, $p = .002$, with less sticky fixations in the non-competition (0.8%) than in the competition condition (3.3%). Proportions of sticky fixations under competition decreased with age (*Figure 6.2*) but the interaction of condition and age was not significant, $z = -1.32$, $p = .187$.

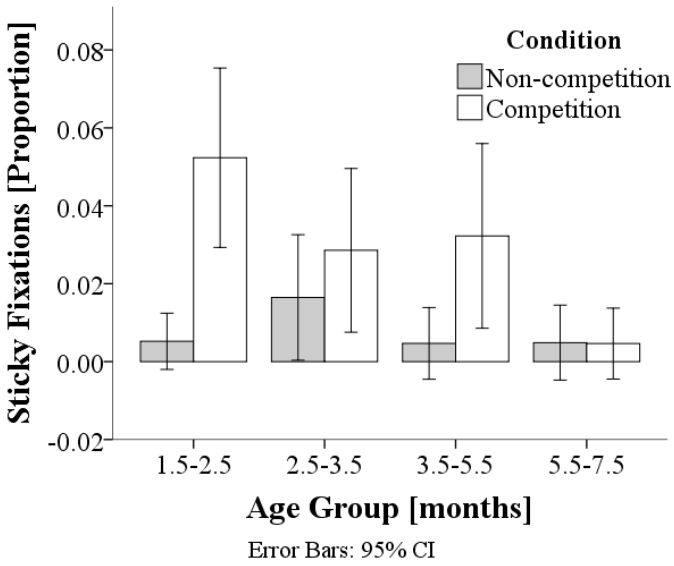


Figure 6.2. Proportion of sticky fixations. The proportion of sticky fixations is greater under competition and decreases with age.

Saccade latency

Histograms of saccade latencies by age and condition are displayed in Appendix O. To investigate differences in saccade latencies between conditions, a linear mixed model was computed, including participants as random effects and condition (non-competition or competition), number of stimuli (1 or 2), screen side watched (left or right) and age group (1.5-2.5, 2.5-3.5, 3.5-5.5 or 5.5-7.5 months) as fixed factors. It showed significant main effects of condition, $F(1, 1694) = 54.44$, $p < .001$, $d = 0.412$, with shorter latencies in the non-competition ($M = 0.540$ sec, $SD = 505$) than in the competition condition ($M = 0.792$ sec, $SD = 0.701$), and number of stimuli, $F(1, 1692) = 15.87$, $p < .001$, $d = 0.158$, with shorter latencies to single targets ($M = 0.630$ sec, $SD = 0.589$) than to double targets ($M = 0.730$ sec, $SD = 0.675$). There was an interaction of age group and condition, $F(3, 1694) = 13.38$, $p < .001$, showing that saccade latencies in competition but not in non-competition conditions decreased with age (*Figure 6.3*).

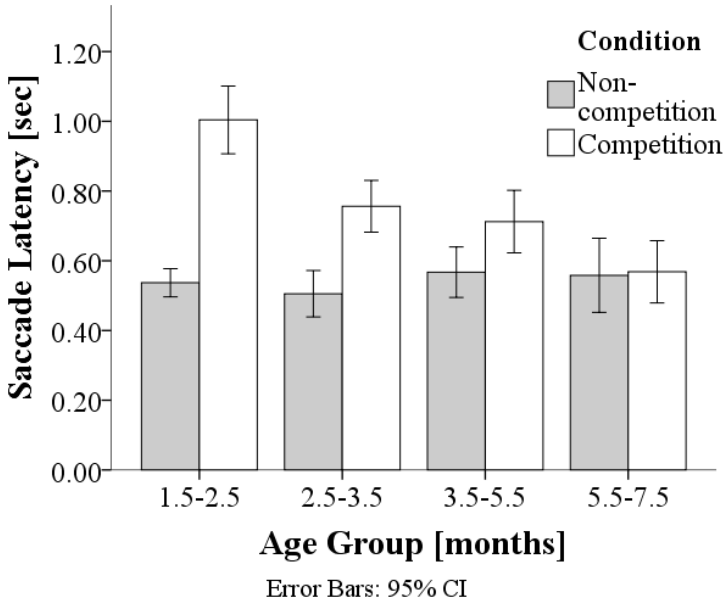


Figure 6.3. Changes in saccade latencies. Saccade latencies decrease with age in the competition condition but remain constant in the non-competition condition.

In summary, the proportion of sticky fixations was higher and mean saccade latencies were longer in competition than in non-competition conditions and both decreased with age. Saccade latencies were shorter towards single than towards double targets.

6.3.3 Neural results

Appendix J displays all topographical plots of the responses observed for infant subjects. The most prominent responses for all age groups within the extracted time window were a widespread anterior positivity, coinciding with a posterior negativity (*Figure 6.4*). Detailed plots of the wave forms in frontal and occipital areas can be found in Appendix K.

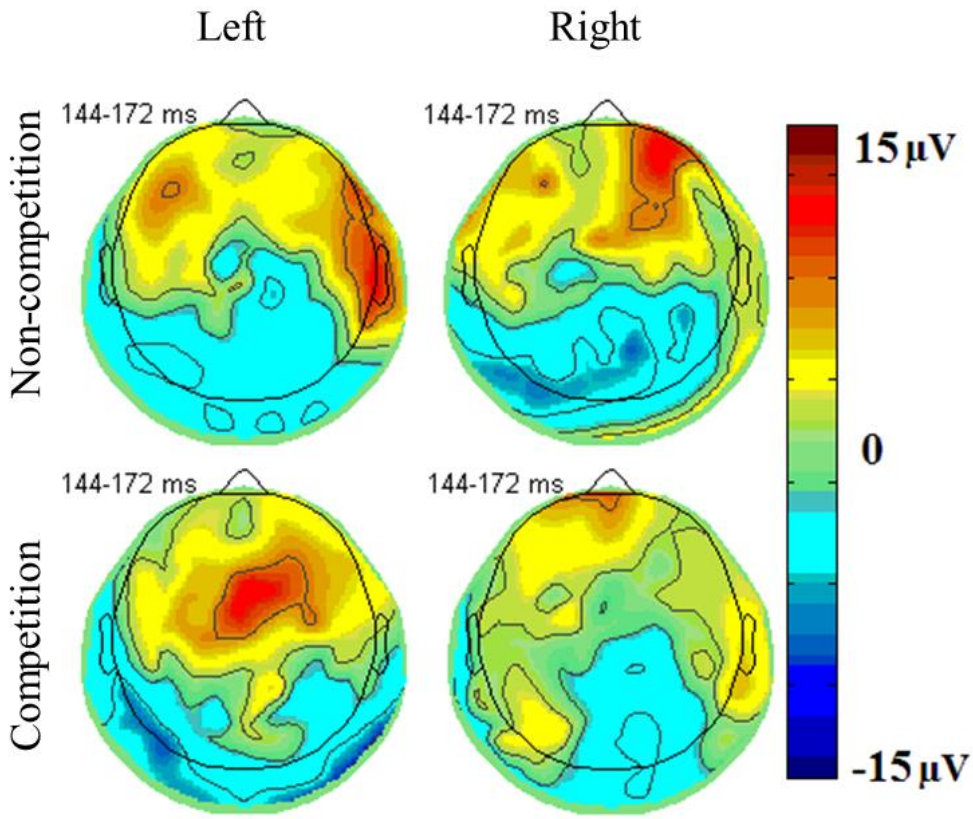


Figure 6.4. Topographical plots of neural responses. Prominent responses after target onset include an anterior positivity and a posterior negativity that are similar for targets on the left (left plots) and right (right plots) screen side and similar in non-competition (top) and competition (bottom) conditions. This plot displays example data from infants between 5.5 and 7.5 months, but similar responses were found for all age groups (Appendix J).

Data processing and analysis

To avoid artefacts, the following analyses were executed on the subset of infants who completed at least 5 successful trials in every condition, meaning that they made a correct response without data loss from either the eye-tracker or the EEG (section 6.2.1). Only single target conditions are described in the following, as subjects completed more of them successfully. An additional analysis of data of all infants (including the subjects that were excluded from the analysis according to the strict criteria) and double target conditions is reported in Appendix L.

Mean amplitudes in frontal and occipital areas were calculated for 50 ms intervals from 0-50 ms, 50-100 ms, 100-150 ms and 150-200 ms and the time window was coded and included as a factor in the analysis. Extreme data points were excluded

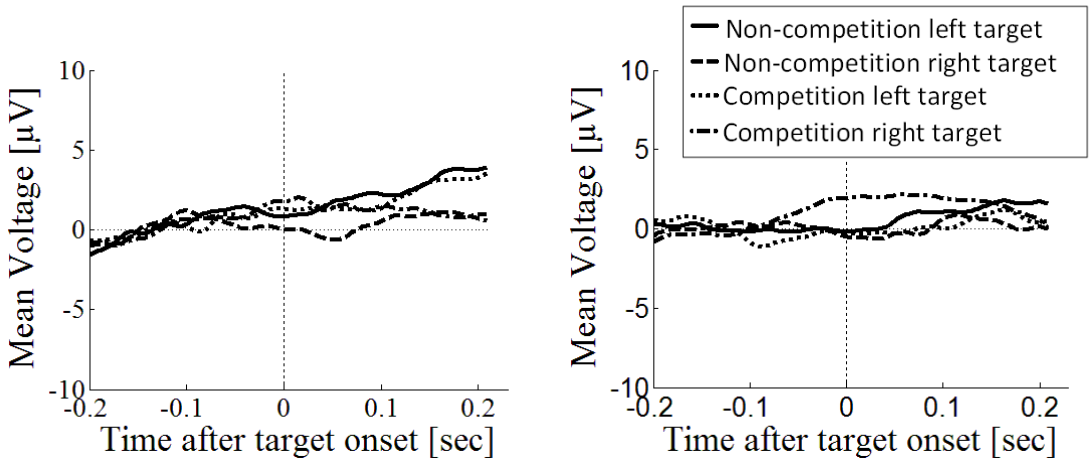
as outliers when they lay outside 1.5 times the interquartile range around the median (e.g. Hubert & Van der Veeken, 2008). The median was used to allow more robust criteria to define extreme outliers (see: Hubert & Van der Veeken, 2008; Rousseeuw & Hubert, 2011). Mixed linear models were computed, including participants as random effects and condition (competition and non-competition), age group, time window and brain hemisphere as fixed factors. As previous research (Csibra et al., 1998) found lateralised responses in frontal areas, the factor brain side (left or right side) was added as a predictor for analyses of frontal response amplitudes.

Frontal response

Frontal responses were extracted in two lateral fronto-central electrode clusters (see Chapter 2, Figure 2.5 and section 2.3.2 for details on the extracted electrodes). Frontal areas show an overall positive response (*Figure 6.5*). Detailed wave plots of frontal responses in all age groups can be found in Appendix K. Response amplitudes increase with age and show more distinguishable peaks within the extracted epoch (0 to 230 ms after target onset) in older infants (*Figure 6.5*b).

1.5-2.5 months

a) Left Hemisphere **Right Hemisphere**



5.5 to 7.5 months

b) Left Hemisphere **Right Hemisphere**

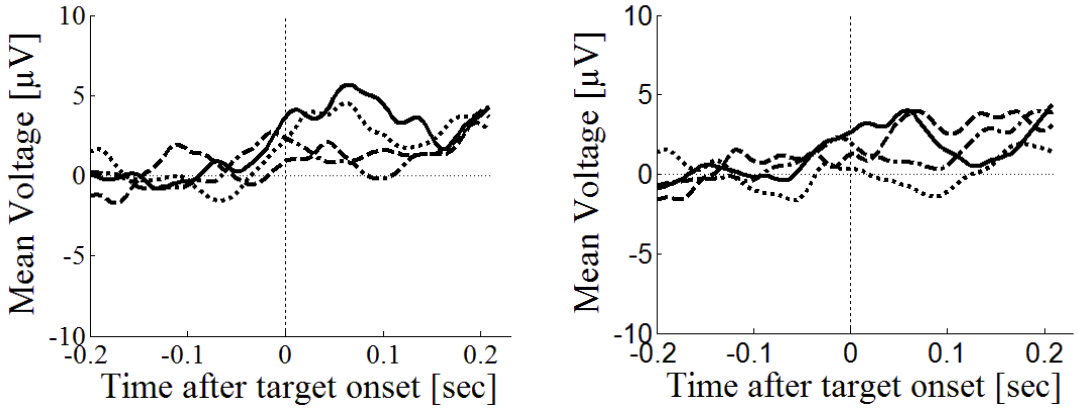


Figure 6.5. Wave plots of frontal responses. Waves in frontal areas show an overall positive response in the left (left) and right (right) brain hemisphere, which contains more different peaks in infants between 5.5 and 7.5 months (bottom) than in infants between 1.5 and 2.5 months (top). Detailed plots of different age groups are displayed in Appendix K.

The frontal response had a median amplitude of 1.18 µV (*25th percentile* = -2.23, *75th percentile* = 4.80, *interquartile range* = 7.04). A linear mixed model showed a marginal effect of hemisphere, $F(1, 722) = 3.16$, $p = .076$, $d = 0.149$, with smaller amplitudes in the ipsilateral ($M = 0.82$, $SD = 4.41$) than in the contralateral hemisphere ($M = 1.49$, $SD = 4.53$). There was a significant interaction of condition and age group,

$F(3, 726) = 3.97$, $p = .008$, showing an increase of amplitude with age in the non-competition condition but a decrease in the competition condition (*Figure 6.6*). Note that younger age groups (1.5-5.5 months) showed greater amplitudes in the competition than in the non-competition condition, while only the oldest age group (5.5-7.5 months) showed greater amplitudes in the non-competition condition ($M = 2.30$, $SD = 4.56$) than in the competition condition ($M = 0.73$, $SD = 4.94$), $F(1, 145) = 9.50$, $p = .002$ (*Figure 6.6*). In addition there was a significant interaction of hemisphere and age group, $F(3, 722) = 6.33$, $p < .001$, showing that ipsilateral activation increased with age, while contralateral activation decreased (*Figure 6.7*), and a significant three-way interaction of condition, hemisphere and age group, $F(3, 723) = 2.70$, $p = .045$, showing that contralateral activity decreased with age in the competition condition, while ipsilateral activity increased with age in the non-competition condition (*Figure 6.8*).

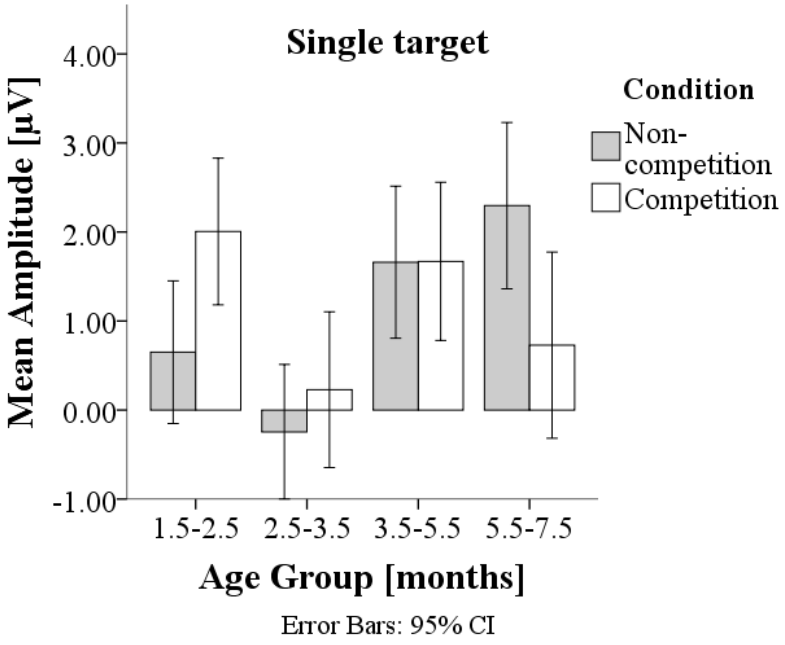


Figure 6.6. Interaction effect of age group and condition on mean frontal amplitude. The mean amplitude in frontal areas increases with age in the non-competition condition, while it decreases with age in the competition condition.

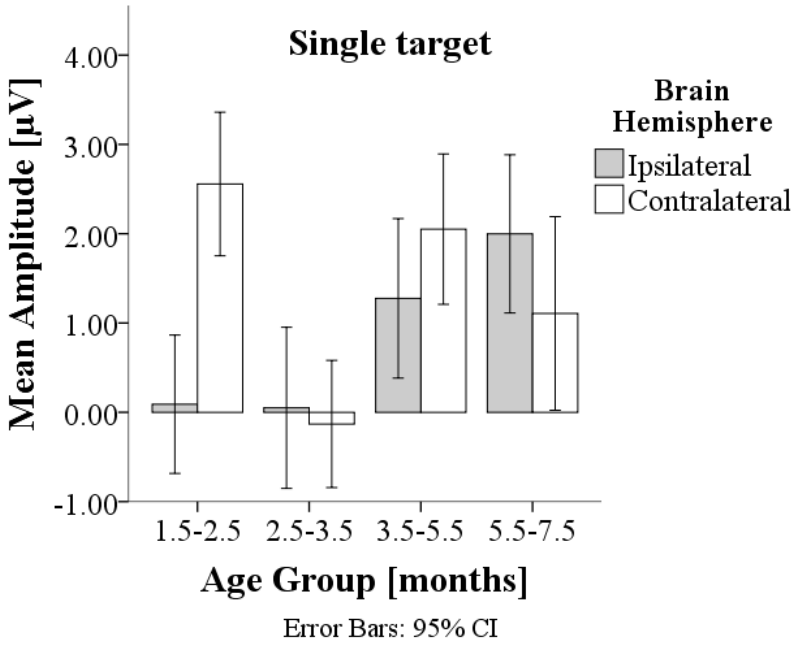


Figure 6.7. Interaction effect of age group and hemisphere on mean frontal amplitude. Mean amplitudes in the contralateral hemisphere decrease with age, while mean amplitudes in the ipsilateral hemisphere increase with age.

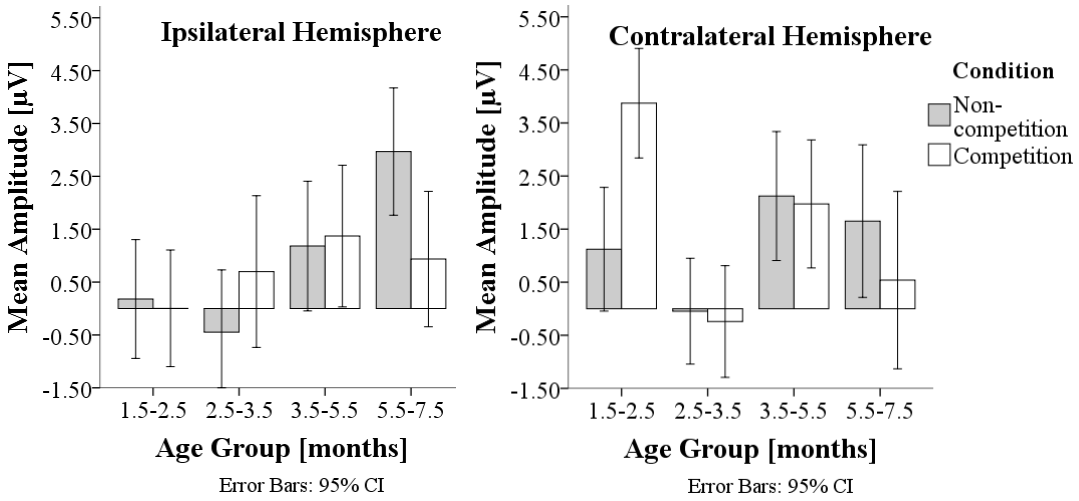


Figure 6.8. Three-way interaction effect of age group, hemisphere and condition on mean frontal amplitude. Developmental changes are driven by an increase in ipsilateral amplitudes in the non-competition condition that coincides with a decrease in contralateral amplitudes in the competition condition.

After adding the factor brain side (left or right) to the analysis, previous effects were confirmed and there was an additional interaction effect of condition and brain side, $F(1, 658) = 3.97$, $p = .047$, showing greater amplitudes in the competition

condition in the left and greater amplitudes for the non-competition condition in the right brain side (*Figure 6.9*). There was an interaction of brain side and age group, $F(3, 658) = 3.19$, $p = .023$, with increasing amplitudes in the right brain side with age (*Figure 6.10*). A three-way interaction of brain hemisphere, brain side and age group, $F(3, 661) = 8.37$, $p < .001$, showed an increase with age in the left brain side when it was ipsilateral and an increase in the right side when it was contralateral. Finally, there was a four-way interaction of condition, hemisphere, brain side and age group, $F(3, 659) = 8.07$, $p < .001$.

In summary, frontal response amplitudes show various interaction effects with age. Amplitudes in the non-competition condition and in the ipsilateral hemisphere increase with age (particularly if this is the left brain side); while amplitudes in the competition condition and in the contralateral hemisphere decrease with age, particularly in the right brain side.

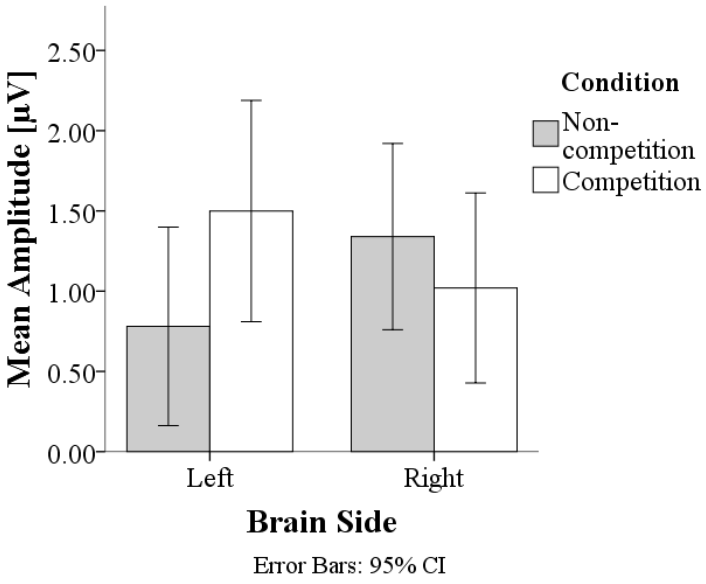


Figure 6.9. Interaction effect of brain side and condition on mean frontal amplitude. Amplitudes in the left brain side are greater in competition and amplitudes in the right brain side greater in non-competition conditions.

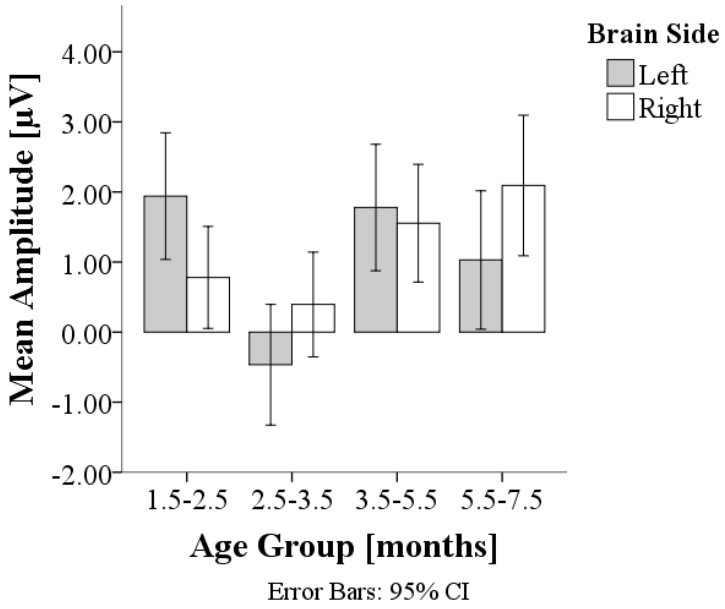


Figure 6.10. Interaction effect of age group and brain side on mean frontal amplitude. Amplitudes in the right brain hemisphere increase with age.

Occipital response

Responses were extracted in two lateral occipital electrode clusters around the electrode locations O1 and O2 (see Chapter 2, Figure 2.4 and section 2.3.2 for details on the extracted electrodes). Detailed wave plots of the occipital response are displayed in Appendix K. Response amplitudes are greater in older infants and show more distinguishable peaks within the extracted epoch than in younger infants. Older infants showed a complex of a negative – positive – negative local peak within the time window, including a negative peak around 80 ms post target, a more positive response around 150 ms and a greater negativity around 200 ms post target. This complex was not visible in younger infants (*Figure 6.11*).

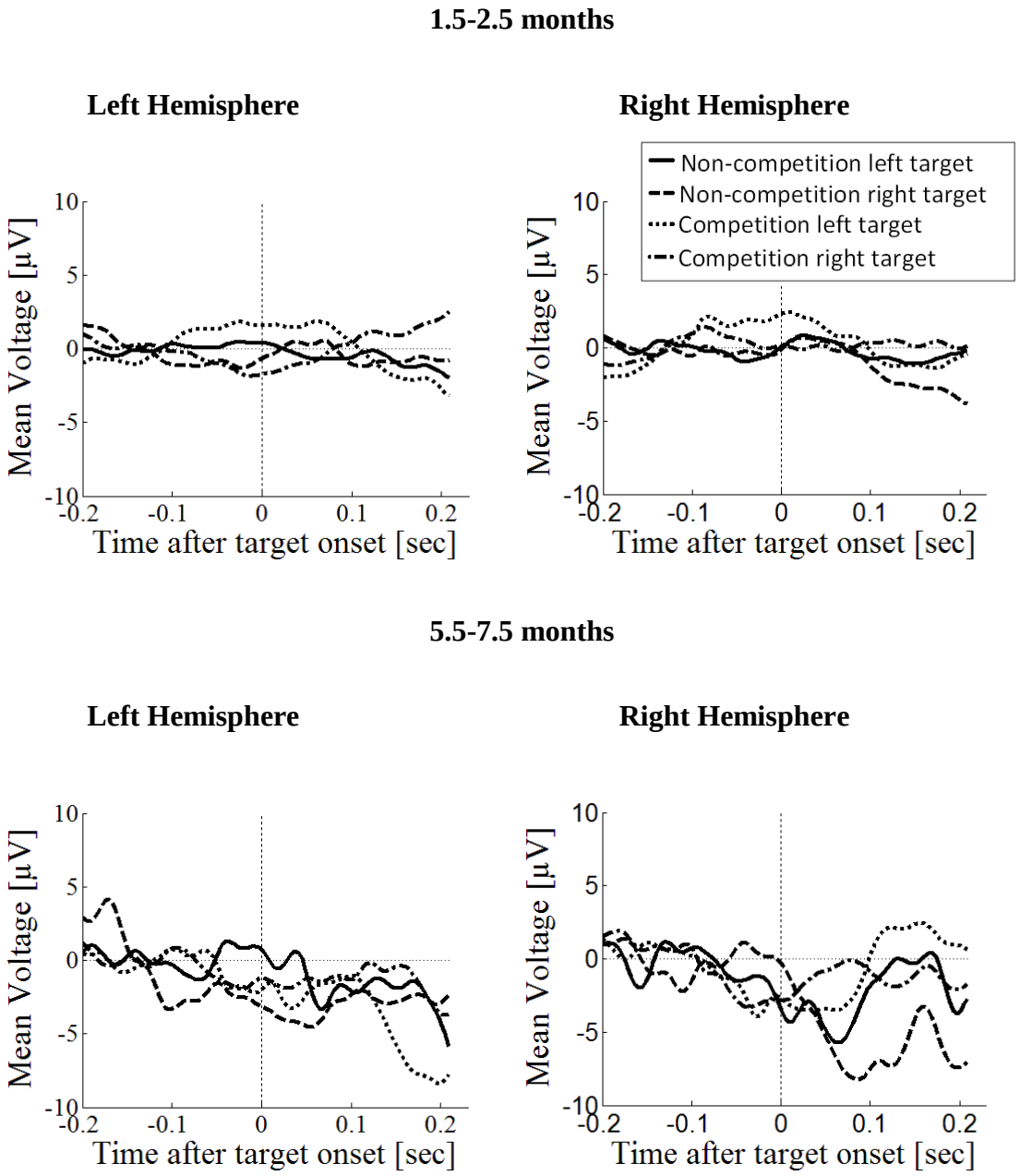


Figure 6.11. Wave plots of occipital responses. Waves in occipital areas show an overall negative response in the left (left) and right (right) brain hemisphere that contains more different and earlier peaks in infants between 5.5 and 7.5 months (bottom) than in infants between 1.5 and 2.5 months (top).

The posterior response had a median amplitude of -0.82 µV, (*25th percentile* = -5.22, *75th percentile* = 3.69, *interquartile range* = 8.91). A linear mixed model showed a significant interaction effect condition and age group, $F(3, 630) = 2.68$, $p = .046$, showing an increase in amplitude with age that starts at an earlier age in the competition condition than in the non-competition condition (*Figure 6.12*). There was an interaction of hemisphere and age group, $F(3, 626) = 3.47$, $p = .016$, showing an increase in

amplitudes with age that begins in contralateral hemispheres first, followed by ipsilateral hemispheres (*Figure 6.13*).

In summary, occipital areas show more distinct response components in older infants than in younger infants. Occipital response amplitudes increase with age and the increase occurs at an earlier age in the competition than in the non-competition condition and at an earlier age in the contralateral than in the ipsilateral hemisphere.

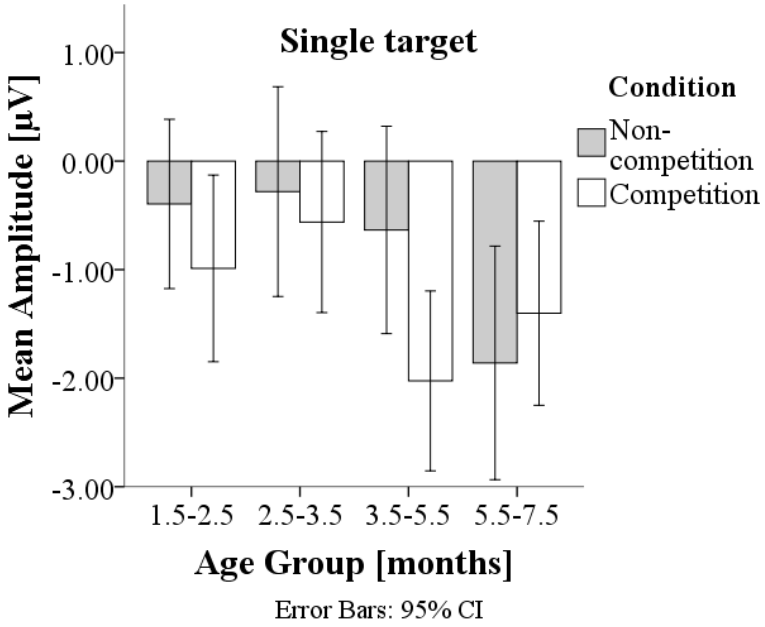


Figure 6.12. Interaction effect of age group and condition on mean occipital amplitude. Mean amplitudes of the posterior negativity increase with age. The increase occurs in competition conditions first (around 3.5-5.5 months) followed by non-competition conditions (around 5.5-7.5 months).

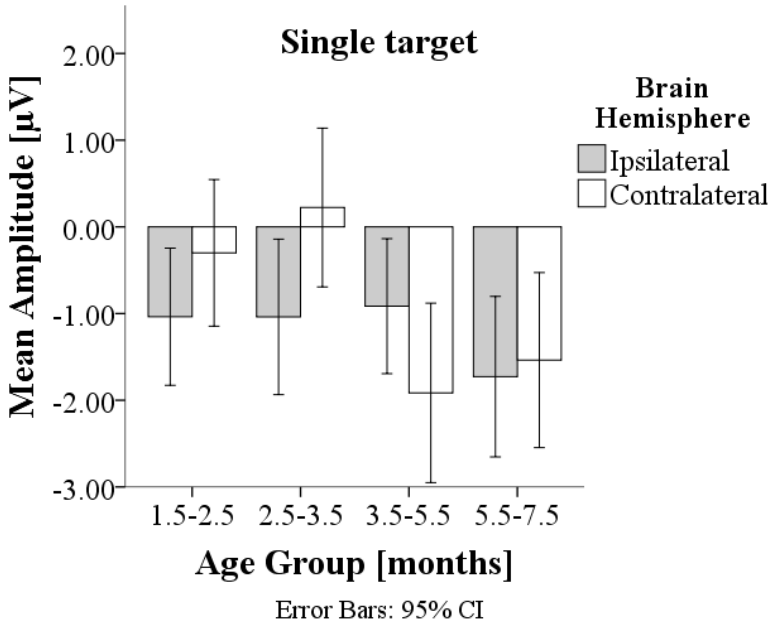


Figure 6.13. Interaction effect of age group and hemisphere on mean occipital amplitude. Mean amplitudes of the posterior negativity increase with age and the increase occurs in the contralateral hemisphere first (3.5-5.5 months), followed by the ipsilateral hemisphere between 5.5 and 7.5 months.

6.3.4 Neural responses during sticky fixations

Data processing and analysis

To investigate differences in neural mechanisms during successful re-fixation compared to sticky fixations as a failure to re-fixate (i.e. the effect of the factor "stickiness" on responses), infants who showed sticky fixations during the experiment were selected (n = 36, M_{age} = 3.24, SD = 1.65). They showed no significant differences to the infants selected for the previous EEG analysis in noise threshold (M = 35.4 µV, SD = 18.2), $t(61) = 0.83$, p = .411, or range threshold (M = 126 µV, SD = 65.8), $t(61) = 0.78$, p = .436; however the overall trial number was smaller with on the whole 153 noise-free trials with sticky fixations (within subjects: M = 3.33 trials, SD = 2.95).

Topographical plots of the response during sticky fixations did not show the clear anterior positivity – posterior negativity pattern that was observed for correct re-fixations, but slightly more positive responses in posterior areas (*Figure 6.14*).

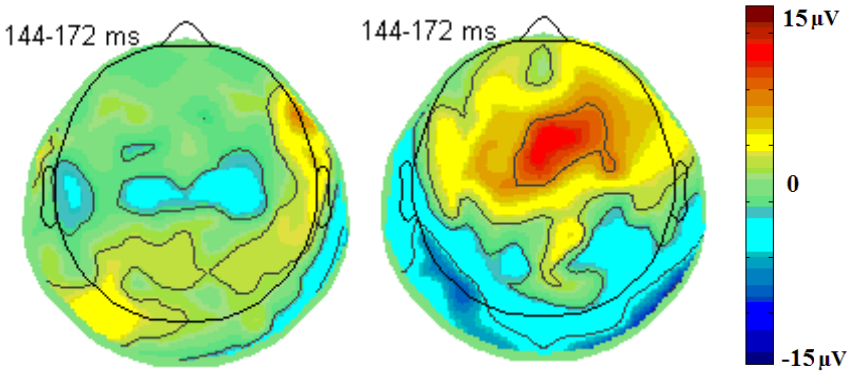


Figure 6.14. Topographical plots of conditions with sticky fixations and correct re-fixations. Responses after target onset during sticky fixations (left) show no clear frontal positivity and posterior negativity like correct re-fixations (right). The plot displayed shows left competition conditions, but similar responses occur in all conditions.

Frontal response

The overall frontal median amplitude was 0.84 µV (25^{th} *percentile* = -3.34, 75^{th} *percentile* = 5.51, *interquartile range* = 8.86). After excluding outliers and double target conditions, a linear mixed model was computed, including participants as random effects and condition, hemisphere, time window and "stickiness" (sticky fixation or correct re-fixation) as fixed factors. It showed a significant effect of condition, $F(1, 1102) = 5.66$, $p = .018$, $d = 0.070$, with higher amplitudes in the competition condition ($M = 1.22$, $SD = 5.62$) than in the non-competition condition ($M = 0.85$, $SD = 4.85$), and a significant effect of hemisphere, $F(1, 1068) = 4.53$, $p = .033$, $d = 0.166$, with greater amplitudes in the contralateral ($M = 1.50$, $SD = 5.42$) than in the ipsilateral hemisphere ($M = 0.62$, $SD = 5.17$). There was a marginal interaction of condition and time window, $F(3, 1065) = 2.16$, $p = .091$, with increasing amplitudes over time in the competition but not in the non-competition condition (*Figure 6.15*), a marginal interaction of condition and "stickiness", $F(1, 1102) = 3.43$, $p = .064$, with greater amplitudes for successful re-fixations than for sticky fixations, and greater responses in the competition condition (*Figure 6.16*), and a significant interaction of time window and response correctness, $F(3, 1065) = 3.09$, $p = .027$, showing increasing amplitudes over time for correct re-fixations compared to decreasing amplitudes over time for sticky fixations (*Figure 6.17*).

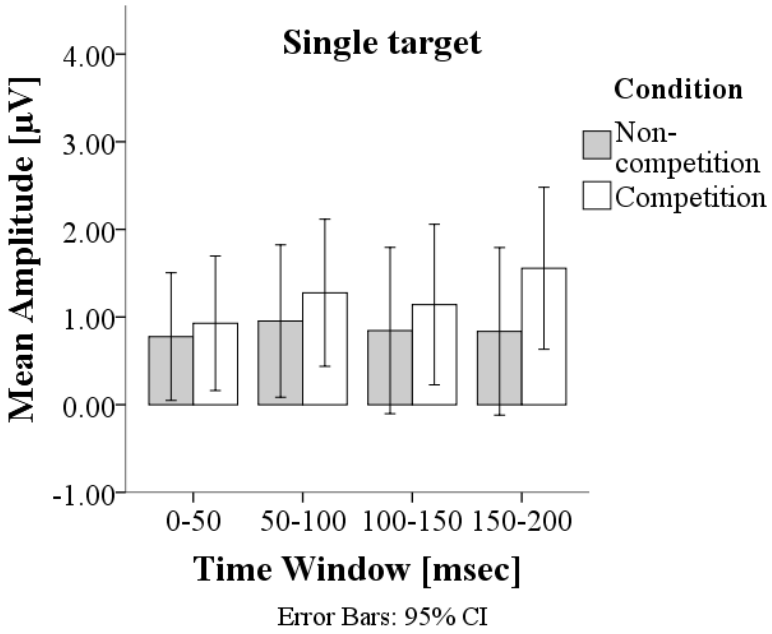


Figure 6.15. Interaction effect of time window and condition on mean frontal amplitude. Mean amplitude increases over time in the competition condition, but not in the non-competition condition.

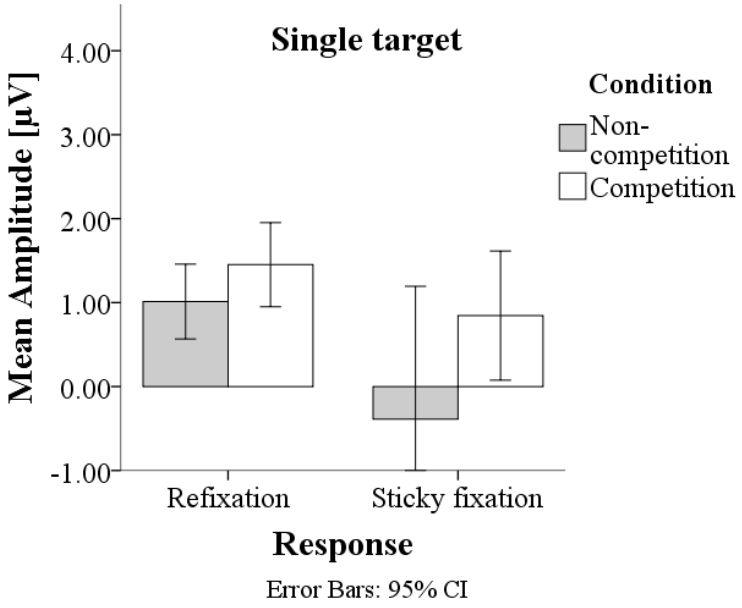


Figure 6.16. Interaction effect of response and condition on mean frontal amplitude. Mean amplitudes in frontal areas are greater for correct re-fixations than for sticky fixations and they are greater in the competition condition than in the non-competition condition.

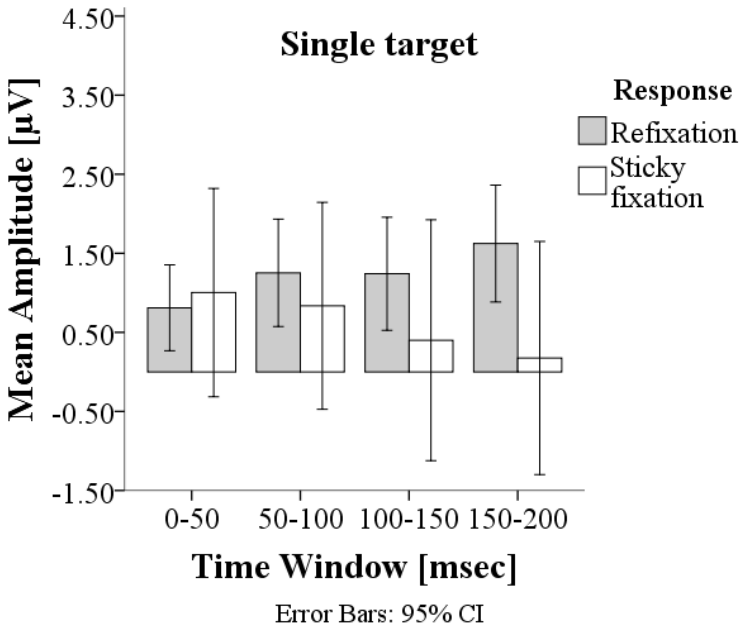


Figure 6.17. Interaction effect of time window and response on mean frontal amplitude. Mean amplitudes increase over time for correct re-fixations, while they decrease for sticky fixations.

To investigate changes in the observed effects with age, the factor age group was added to the model, with the other fixed factors remaining. It showed a significant effect of "stickiness", $F(1, 1030) = 4.57$, $p = .033$, $d = 0.117$, with smaller amplitudes for sticky fixations ($M = 0.63$, $SD = 5.31$) than for correct re-fixations ($M = 1.23$, $SD = 4.94$), and a significant main effect of age, $F(3, 1030) = 11.97$, $p < .001$, with greater amplitudes in older infants (Table 6.4). There was a significant interaction of "stickiness" and age, $F(3, 1030) = 7.99$, $p < .001$, showing increasing overall amplitudes with age for sticky fixations but not for correct re-fixations (*Figure 6.18*). A marginal three-way interaction of hemisphere, "stickiness" and age, $F(3, 1030) = 2.10$, $p = .099$, showed that the increase in amplitude with age for sticky fixations mainly occurred in the ipsilateral hemisphere (*Figure 6.19*).

In summary, fronto-central response amplitudes were smaller for sticky fixations than for correct re-fixations. When infants failed to shift attention, their frontal responses decreased over time, while frontal amplitudes increased over time before successful re-fixations. Contralateral response amplitudes were greater than ipsilateral amplitudes, but ipsilateral amplitudes increased with age. Furthermore, frontal responses were greater in competition than in non-competition conditions.

Table 6.4. *Mean amplitudes in frontal areas are smaller in infants under 3.5 months than in infants older than 3.5 months, possibly because they more commonly show sticky fixations.*

Age group	M	SD
1.5-2.5 months	0.62	5.48
2.5-3.5 months	0.18	5.18
3.5-5.5 months	2.27	4.99
5.5-7.5 months	1.78	5.22

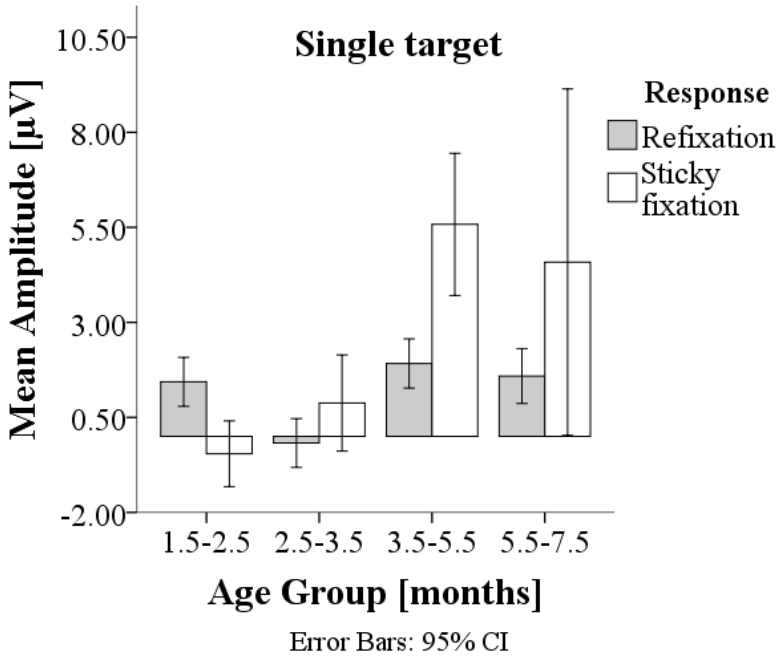


Figure 6.18. Interaction effect of age group and "stickiness" on mean frontal amplitude. Mean amplitudes during sticky fixations increase with age, while mean amplitudes for correct re-fixations remain constant with age.

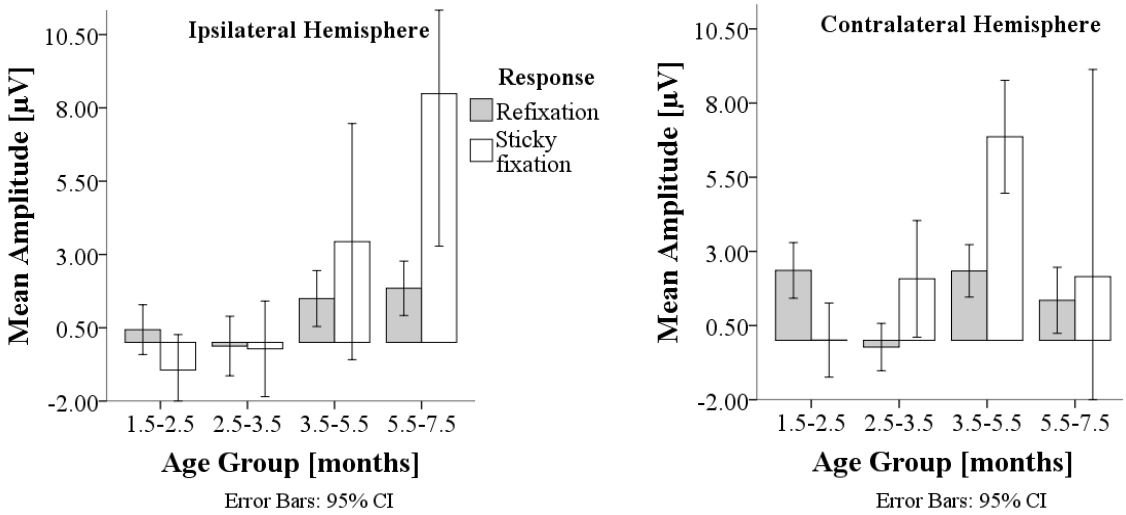


Figure 6.19. Three-way interaction effect of hemisphere, age group and "stickiness" on mean frontal amplitude. Mean amplitudes increase with age for sticky fixations but not for correct re-fixations, especially in the ipsilateral hemisphere.

Occipital response

The median response in occipital areas was -0.84 µV (*SD* = 12.75, *25th percentile* = -6.06, *75th percentile* = 4.16, *interquartile range* = 10.22. After excluding outliers and double target conditions, a linear mixed model was computed, including participants as random effects and condition, hemisphere, time window and "stickiness" (correct re-fixation or sticky fixation) as fixed factors. It showed no significant main or interaction effects.

To investigate changes in the observed effects with age, the analysis was repeated after adding the factor age group to the model. It showed a marginal interaction of hemisphere and time window, showing a marginal increase in ipsilateral amplitudes over time, $F(3, 835) = 2.45$, $p = .062$, *Figure 6.20*, a significant interaction of hemisphere and age group, $F(3, 841) = 4.80$, $p = .003$, *Figure 6.21*, and a three-way interaction of hemisphere, time window and "stickiness", $F(3, 835) = 3.21$, $p = .023$, *Figure 6.22*.

In summary, occipital response amplitudes showed no significant effects unless the factor age group was included in the analysis. The age group between 2.5 and 3.5 months differed from other age groups in lateralisation of the response and response amplitudes varied more across time for sticky fixations than for correct re-fixations.

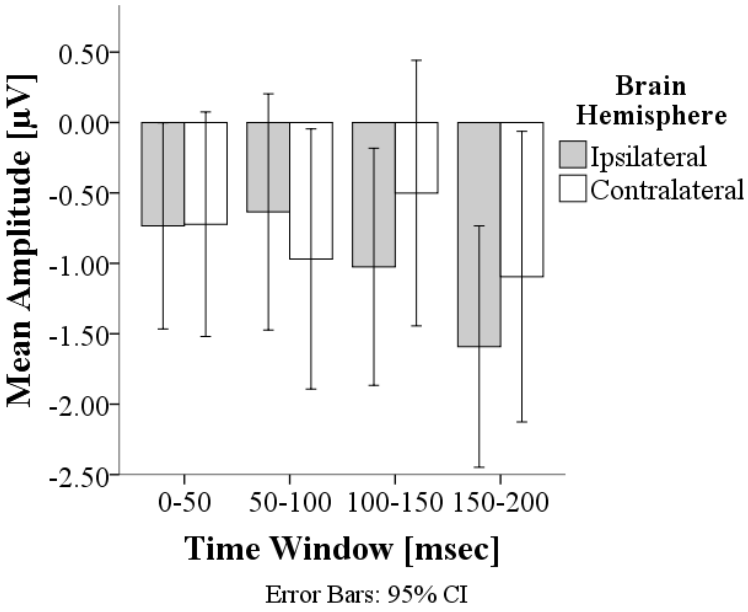


Figure 6.20. Interaction effect of time window and brain hemisphere on mean occipital amplitude. Mean amplitudes increase over time, especially in the ipsilateral hemisphere.

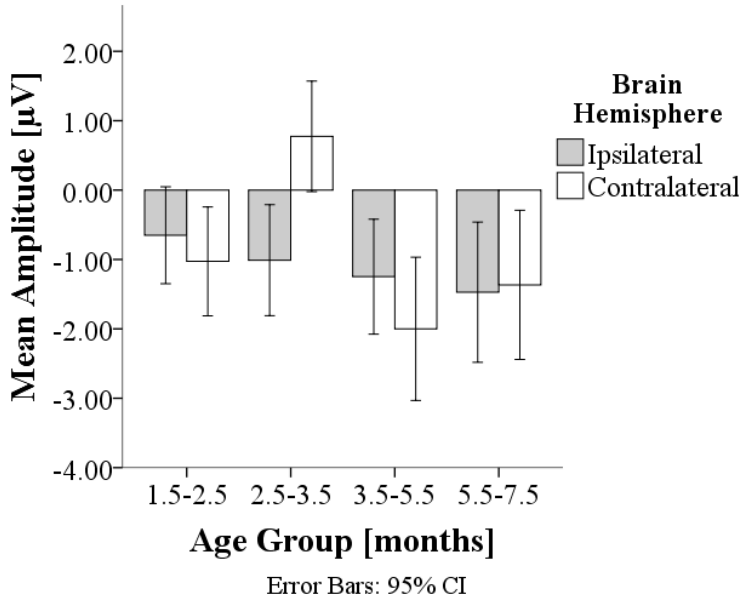


Figure 6.21. Interaction effect of age group and hemisphere on mean occipital amplitude. Amplitudes increase with age, with an exception of decreasing contralateral amplitudes between 2.5 and 3.5 months.

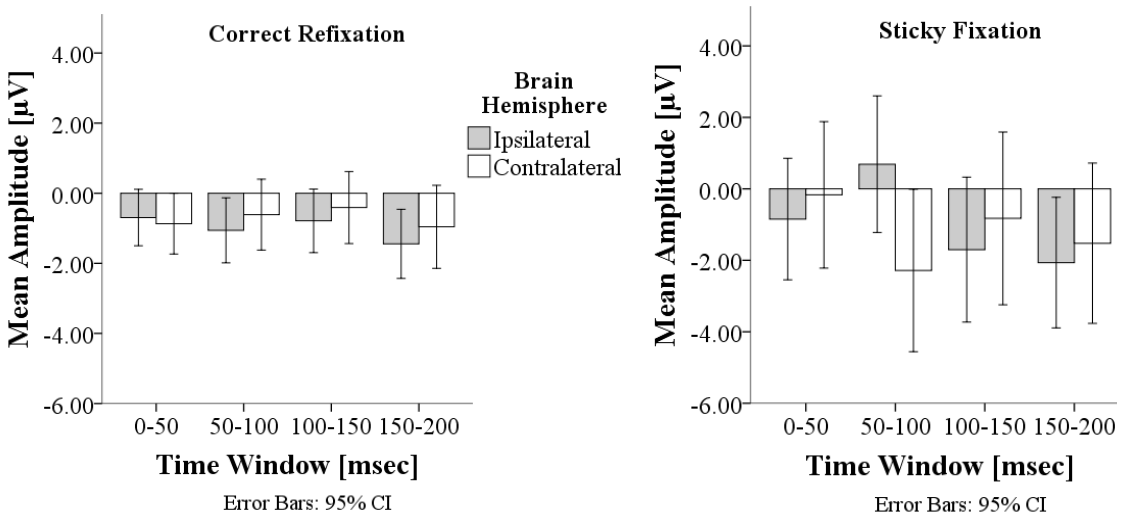


Figure 6.22. Three way interaction effect of time window, hemisphere and "stickiness" on mean occipital amplitude. Correct re-fixations show a consistent pattern of amplitudes over time, while a greater contralateral response is visible between 50 and 100 ms for sticky fixations.

6.4 Discussion

This study aimed at investigating neural mechanisms of attention shifts in infants between 1 and 8 months of age. It was predicted that infants show slower saccade latencies and more sticky fixations in competition than in non-competition conditions and that the ability to shift under competition improves with age due to developing neural mechanisms for disengagement. It was furthermore expected that differences in the ability to shift under competition become visible on a neural level, with posterior areas involved from an early age, while frontal areas increasingly become involved from 3 months onwards. Presuming that the frontal cortex is involved in attentional control, sticky fixations were predicted to involve less frontal activation as a sign of immature cortical control mechanisms.

6.4.1 Behavioural responses

Saccade latencies were significantly longer in the competition condition than in the non-competition condition, and latencies under competition significantly decreased with age. These findings replicate eye-tracking results from Chapter 3 and are in line with previous research demonstrating longer saccade latencies when disengagement from a central stimulus is required, using the FSP (e.g. Atkinson & Braddick, 2012; Atkinson et al., 1988; Atkinson et al., 1992; Butcher et al., 2000; Hood & Atkinson,

1993) and the gap paradigm (e.g. Colombo, 2001; Elsabbagh et al., 2013; Elsabbagh et al., 2009; Farroni et al., 1999; M. H. Johnson et al., 1991; Matsuzawa & Shimojo, 1997).

The majority of trials (84%) included correct re-fixations, suggesting that the data quality collected by the eye-tracker was high. Around 2% of trials were sticky fixations, decreasing from more than 5% under 2.5 months of age down to almost 0% at 5.5 months. This is a similar pattern to the results for saccade latencies, being higher under competition und decreasing with age. In line with previous research, sticky fixations were most prominent in very young infants (Atkinson et al., 1992), however this effect was not significant in the mixed logistic regression analysis.

The observed behavioural effects were similar when only infants who met the criteria for EEG data inclusion (i.e. higher number of successful trials) or all infants (Appendix I) were included in the analysis, suggesting that the behavioural method leads to robust findings, even with few or noisy trials.

6.4.2 Neural responses

The most prominent brain responses included a frontal positivity, which was in line with findings from Csibra et al. (1998) in the gap paradigm, and a posterior negativity. It is possible that the frontal positivity and occipital negativity are two ends of the same dipole. However, they are differently affected by conditions, as will be discussed in the following sections, suggesting that more than one dipole is underlying the observed effects. Responses in older infants were similar to the ones observed in 6 months old infants by Csibra et al. (1998), while younger infants differed, particularly in posterior responses (see Table 6.5 for a brief overview). Neural findings will be discussed in regards to the previous literature and in regards to attention models.

Table 6.5. *Comparison of target-locked ERPs observed in the gap paradigm in 6 months old infants by Csibra et al. (1998) and on 1.5 to 7.5 months old infants in the current study of the FSP.*

Response	**Csibra et al. (1998), 6 months**	**Current study < 5.5 months**	**Current study > 5.5 months**
Frontal positivity	Yes	Yes	Yes
Occipital negative-positive-negative response pattern	Yes	No	Yes

Frontal positivity

Amplitudes of the frontal positivity were generally marginally greater in the contralateral than in the ipsilateral hemisphere. Overall activity in the contralateral hemisphere decreased with age, while ipsilateral activity increased with age. This change from contra- to ipsilateral may reflect the development of interhemispheric connections. While visual information is automatically processed on the contralateral hemisphere from early on, the interhemispheric connections are still developing during infancy, leading to increasing ipsilateral processing. This connection hypothesis is in line with He et al. (2007) suggesting that connections between parietal hemispheres play a crucial role for attention shifts in neglect patients. In infants, intra-cortical connections are not yet fully developed (e.g. Huttenlocher, 2002; M. H. Johnson, 2002), leading to an impaired ability to shift attention. The change in lateralisation of neural responses with age recorded in this study provides support to the idea that intra-cortical connections play a crucial role in attention development. It would be interesting to use functional magnetic resonance imaging (fMRI) in infants in the future (when fMRI technology becomes more infant friendly, see discussion in Chapter 7, section 7.2.4) to see if the differences in anterior activation coincide with a similar impairment in interconnectivity as in neglect patients (He et al., 2007).

Furthermore, there was a three-way interaction of condition, hemisphere and age group, showing that the decrease in contralateral activity with age was greater in the competition condition, while ipsilateral activity increases with age were greater in the non-competition condition. Overall, amplitudes in the competition condition decreased

with age, while amplitudes in the non-competition condition increased with age. Interestingly, the younger age groups (1.5-5.5 months) showed greater amplitudes in the competition than in the non-competition condition, while only the oldest age group (5.5-7.5 months) showed greater amplitudes in the non-competition condition than in the competition condition. Previous findings from Csibra et al. (1998) found greater frontal amplitudes in the gap than in the overlap condition. This finding was replicated in the oldest age group tested here, but not in younger infants. One possible explanation for these interaction effects is that different overlapping mechanisms are involved in the responses observed here, as will be discussed in regards to previous literature in the following section.

Csibra et al. (1998) found a frontal positivity between 80 and 200 ms after target onset in 6 months old infants. As the FSP is highly similar to the gap task used by Csibra et al. (1998), the frontal positivity observed in this study is likely to reflect similar mechanisms as observed in previous target-locked ERPs. In addition to this target-locked response, Richards (2001c) found an anterior positivity preceding saccades by 50 ms from 5 months of age (in: Richards, 2005). As this response evolves after 20 weeks of age it should mainly be visible in the older age groups tested for this study. In particular, saccade latencies in this study decreased with age, meaning that saccade-linked potentials were more likely to occur in the extracted epoch in older infants than in younger infants. Furthermore, models by Corbetta and Shulman (2002, 2011) suggest a right-lateralised frontal attention network to be involved in attention shifts in adults, as reviewed in Chapter 1, section 1.4.3. Greater amplitudes in non-competition than in competition conditions may be due to an overlap of the target-locked responses with a right-lateralised saccade-locked response in older infants. In young infants saccade latencies are significantly longer, making it less likely for saccade-locked responses to fall within the extracted time-window. Therefore, younger infants show more clear target-locked responses, which were found to be higher in the competition than in the non-competition condition, possibly reflecting additional activation required to initiate shifts under disengagement.

Another finding supporting the idea of two different components overlapping in the observed response is that there were greater amplitudes in the competition condition in the left brain side, and greater amplitudes in the non-competition condition in the right brain side. Furthermore, brain side and age group interacted, with amplitudes in

the right brain side increasing with age and amplitudes in the left brain side decreasing. Both of these findings are in line with the suggestion that two overlapping components, one target-locked and one saccade-locked one lead to the observed responses (visualised in *Figure 6.23*). The saccade-linked anterior positivity described by G. D. Reynolds and Richards (2005) seems more pronounced in the right hemisphere of the brain, the attention-related Nc response has been localised slightly right of the midline by source localisation in infants (G. D. Reynolds & Richards, 2009) and attention network model derived from adult data suggest a right lateralisation of frontal networks for attention shifts (Corbetta & Shulman, 2002, 2011). As latencies are shorter in the non-competition condition than in the competition condition, saccade linked responses are more likely to fall within the extracted time window in non-competition conditions, leading to more right-lateralised responses in the non-competition condition. Comparably, saccades occur earlier in older infants than in younger infants. Hence, the finding that responses become more right-lateralised with age can also be explained by a greater overlap of pre-saccadic responses with the extracted epoch. Table 6.6 summarises the suggestion that two responses may overlap to form the observed effects.

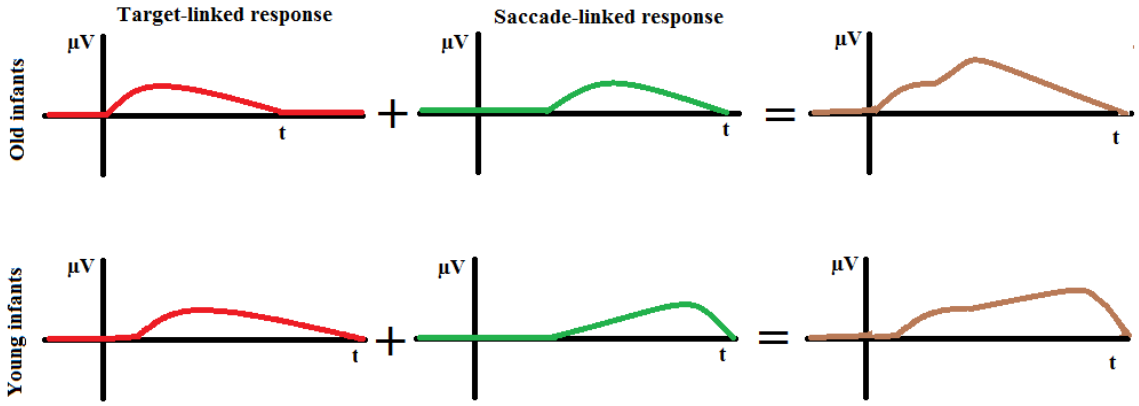


Figure 6.23. Visualisation of the idea that two underlying components form the observed frontal response. Young infants show longer latencies and more widespread components and their saccades (and therefore the saccade-linked responses) occur later.

Table 6.6. *Summary of features of overlapping responses that might be causing the observed findings.*

Response	Lateralization	Effect on findings	Previous literature
Saccade-locked	Right-lateralised	More visible in trials with earlier saccades (i.e. in older infants and in non-competition conditions)	Comparable to pre-saccadic positivity observed by Richards (2001c)
Target-locked	Becoming more ipsilateral with age	Greater in competition than non-competition conditions, possibly reflecting longer disengagement	Comparable to frontal positivity observed by Csibra et al. (1998)

Csibra et al. (1998) tested infants and found greater amplitude differences between conditions in the left than in the right hemisphere, suggesting that the left hemisphere plays a crucial role for disengagement in attention shifts in infants. However, studies on adult patients and models built on adult data have suggested that the right hemisphere plays a crucial role for attention shifts. This prompts the idea that different brain mechanisms are involved in attention shifts in infants and adults. The current study provides data showing that the involvement of the left hemisphere decreases during infancy, coinciding with greater involvement of the right hemisphere, bridging the gap between infant and adult findings.

Mean amplitude was also affected by a three-way interaction of brain hemisphere, brain side and age group, showing an increase with age in the left brain side when it was ipsilateral and an increase in the right side when it was contralateral. This fits both with the idea that target-linked and saccade-linked responses overlap in trials with early saccades and the idea that interhemispheric connections play a crucial role during that development. As the right hemisphere is more affected by saccade-linked responses, the hemispheric differences are less observable here. However, the left side, which is less affected by saccade-linked potentials, clearly shows increasing ipsilateral activity with age, confirming that the contralateral hemisphere is already active at an early age, while interhemispheric connectivity coincides with improved attentional control with age.

Occipital negativity

A posterior negativity was visible in all age groups. In older infants (5.5-7.5 months), the posterior responses showed the negative-positive-negative pattern observed by Csibra et al. (1998) in 6 months old infants, suggesting that the findings in this FSP study are comparable to findings in the gap paradigm. However, younger infants did not show the clear response pattern, but instead their main response consisted of a widespread negativity. Chapter 2 (section 2.2.3) reviewed the ontogeny of visual responses, showing that a posterior negativity is most clearly visible in young infants from birth on (Benavente et al., 2005; Crognale et al., 1997; Ferriss et al., 1967; McCulloch, 2007; Pryds et al., 1989). Therefore, the current findings are in line with the developmental pattern found by previous research. Furthermore, response latencies have been found to decrease during infancy (Barnet et al., 1980; Ellingson et al., 1972; McCulloch, 2007; McCulloch & Skarf, 1991; Nelson & McCleery, 2008). The response pattern observed in older infants begins with a negativity followed by a positivity. Due to latency decreases with age, the positivity may occur later in young infants, falling outside the extracted epoch of 0 to 230 ms after target onset. As discussed in Chapter 2, early saccades can overlap with responses if longer time windows are extracted. In particular, infants vary significantly within the same age group (Barnet et al., 1980; Coch & Gullick, 2011; Eeg-Olofsson, 1980; Ellingson, 1970; Ellingson et al., 1972; McCulloch, 2007; McCulloch & Skarf, 1991; Nelson & McCleery, 2008; Pryds et al., 1989) and saccade latencies show fairly high standard deviations. Due to the variability in saccade latencies, it was not possible to extract a greater ERP time window without risking significant data loss or distortion due to overlap with saccades.

Despite the negative-positive-negative response pattern, the overall negative response amplitude increased with age. Previous research suggests that ERP amplitudes increase until approximately 6 months of age (Barnet et al., 1980). As the oldest age group tested for this study was between 5.5 and 7.5 months old, the pattern of increasing amplitudes with age is in line with previous studies. The increase began at an earlier age in the competition condition than in the non-competition condition. As the same paradigm used in adult subjects (Chapter 5) showed significant differences in posterior responses between conditions, it is possible that the increasing involvement of occipital brain areas in attention shifts plays a crucial role during development.

The increase in amplitudes with age began in contralateral hemispheres first, followed by ipsilateral hemispheres. As described above, the contralateral hemisphere is automatically involved in visual processing from an early age, while interhemispheric connections are still developing. The timing of the increase in response latency observed in this study supports the idea that mechanisms involving the contralateral hemisphere develop earlier, while a later development of ipsilateral responses is in line with a slow development of interhemispheric communication.

Sticky fixations

Frontal positivity

Sticky fixations generally showed noisier responses and the results should be interpreted with caution as there were overall fewer trials with sticky fixations than with successful re-fixations. Trials with sticky fixations did not show the clear frontal positivity that was observed for correct re-fixations, which is in line with the hypothesis. Two alternative explanations can account for smaller frontal amplitudes during sticky fixations observed in this study. In line with models suggesting an involvement of frontal eye fields in attentional control (Atkinson, 1984; M. H. Johnson, 1990), smaller activity during sticky fixations can be interpreted as a failure of the FEF control system leading to an inability to disengage from a fixation target. Alternatively, as suggested above, the frontal response may reflect two overlapping components, one of which is involved in disengagement from the target (target-locked response) and the other one reflects saccade preparation. In line with this idea, smaller amplitudes can also be related to a lack of saccade planning activity, leading to only one positive component being present during sticky fixations, therefore causing smaller overall amplitudes.

Interestingly, the frontal positivity showed a significant interaction of time window and response correctness, with increasing amplitudes over time for correct re-fixations compared to decreasing amplitudes over time for sticky fixations. Saccade-linked responses, involved in eye movement preparation should occur later within the extracted time window. Therefore, the observed patterns suggest that the later part of the observed response may be related to saccade planning and hence is not present during sticky fixations (see visualisation in *Figure 6.24*). Dipole analyses could confirm whether the response observed in this study consists of two different components stemming from different cortical sources. Behavioural research prompted speculations on whether longer saccade latencies in competition conditions are due to disengagement

from the target or an inhibition of saccades (e.g. Hood & Atkinson, 1993). The current findings suggest that, at least for sticky fixations, it is more likely that a failure to initiate a saccade initiates the sticky fixation than a failure to disengage.

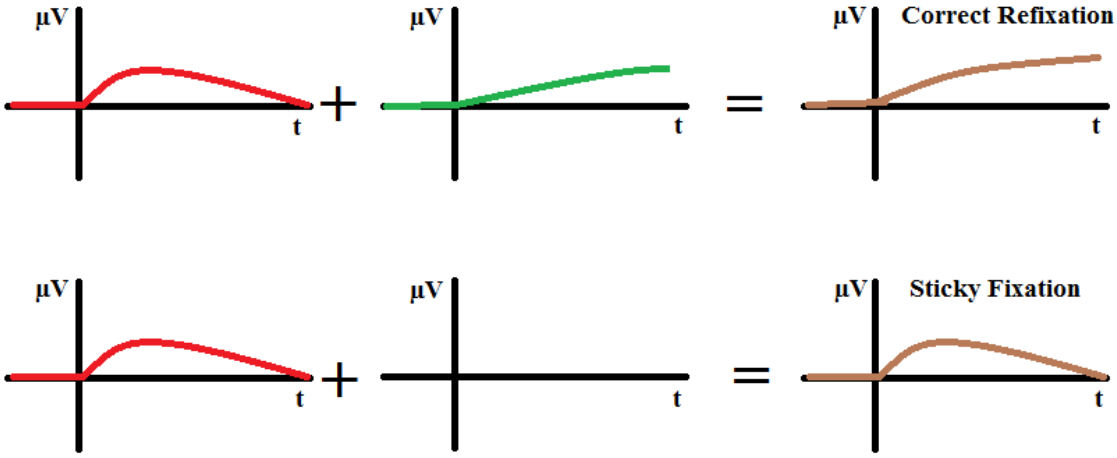


Figure 6.24. Visualisation of the idea that two overlapping components form the observed response during sticky fixations. A target-locked response (left, red) may be involved in disengagement from the stimulus, while a saccade-locked response (middle, green) increases towards the saccade and is only present when saccades are correctly executed (top) but not during sticky fixation trials (bottom). When both components add up, the pattern of increasing responses over time for correct re-fixations and decreasing responses over time for sticky fixations observed in this study results.

The analysis confirmed findings of greater amplitudes in the contralateral hemisphere, which are in line with findings for correct re-fixations, suggesting that they both share an underlying component that depends on developing interhemispheric connections.

When analysing the development of responses with age, the lateralisation significantly changes during development. There was an overall increase in amplitudes with age during sticky fixations, mainly occurring in the ipsilateral hemisphere, while mean amplitudes for correct re-fixations remained constant with age, as contralateral responses decreased while ipsilateral responses increased.

As suggested above, the ipsilateral hemispheric activation may depend on interhemispheric connections and play a crucial role for attention shifts. As for correct re-fixations, the ipsilateral activity during sticky fixations also increases with age. During correct re-fixations the ipsilateral increase coincides with a decrease in

contralateral activity, resulting in a similar overall activation that is more focused over the ipsilateral hemisphere. This lateralisation may be key for the attention shift process to efficiently shift towards one side of the screen. However, during sticky fixations, both hemispheres show an equally high activation, possibly leading to a mutual inhibition of the response. Hence, sticky fixations may result as a failure of neural networks to efficiently focus on one side.

Occipital negativity

There was a trend of ipsilateral amplitudes increasing over time, which, however, was not significant. In line with results on adult subjects in the previous chapters (Chapter 4 and Chapter 5) and previous research on adults subjects (Csibra et al., 1997) the posterior response may shift from the contralateral to the ipsilateral hemisphere.

As observed for correct re-fixations and in line with previous research (e.g. Barnet et al., 1980) the overall amplitude of the occipital negativity increased with age, except for a decrease in contralateral amplitudes between 2.5 and 3.5 months, which was possibly caused by noisy data due to artefacts that have a greater effect on sticky fixations, as they occur less often than correct re-fixations. Particularly the age group between 2.5 and 3.5 months had a tendency to deviate from the overall data trend, showing amplitudes around 0 µV, suggesting that this group may have been more affected by artefacts. During correct re-fixation trials amplitudes were consistently greater in ipsilateral areas, while sticky fixation trials showed greater contralateral amplitudes between 50 and 100 ms, possibly due to noise. Both of these effects may be related to noisy data. Sticky fixations were analysed independent of the number of trials in which they occurred, because they generally occurred less often than correct re-fixations. Therefore, the data quality should be carefully considered before interpreting effects.

6.4.3 Relation to ERPs in infants

The overall shape of ERP waves measured in the current study is in line with previous research on the development of ERPs during infancy. ERP amplitudes increased with age, which has commonly been observed in infants up to 6 months (e.g. Barnet et al., 1980; Hou et al., 2003; Sokol & Dobson, 1976). Furthermore, a greater

number of distinct components was visible in older infants than in younger infants (see also Barnet et al., 1980; Nelson & Luciana, 1998) and the overall response pattern in the oldest age group matched the pattern observed in a similar age group by Csibra et al. (1998). In summary, the current study adds further support to a long list of infant ERP studies showing increasing amplitudes and increasing numbers of response components with age.

6.4.4 Relation to theories of brain development

Bronson (1974) suggests that from the second month of life onwards the cortex is involved in infants' reactions. As the infants in this study were mainly older than 1 month and some target-related brain responses were picked up with EEG in all age groups, the results confirm that cortical mechanisms seem to be involved in attention shifts at this age, which is in line with the hypothesis.

Based on previous models (Atkinson, 1984, 2000a; Bronson, 1974; M. H. Johnson, 1990), frontal responses were expected to increasingly become active between 3 and 6 months. The results show that overall frontal amplitudes remain constant with age; however, significant changes occur regarding the lateralisation of frontal responses. This may suggest that although frontal areas are already active in early infancy, they are less efficiently connected. In particular, ipsilateral activation increases with age, suggesting that ipsilateral activity may be a successful tool to control attention shifts. In adult subjects frontal activation was coinciding with trials in which saccades needed to be inhibited (see Chapter 4 and 5). Ipsilateral activation in frontal areas in infants may reflect an inhibition of the incorrect direction leading to a more effective shift towards the correct direction. FMRI studies in adults (Neggers et al., 2005) suggest that the superior colliculus contains a spatial map and the correct areas of the map need to be activated to initiate a saccade. More lateralised frontal control may more effectively inhibit irrelevant areas of SC, thereby increasing the probability of relevant areas reaching the threshold for saccade execution.

In line with previous models of the development of different attention pathways and from the present data in this thesis it can be suggested that the development of the FEF pathway plays a crucial role during infancy, allowing more efficient control of saccades with progressing development. Occipital areas are also active in infants, but they cannot solely account for all developmental changes observed with age. The *FEF pathway* is

therefore crucial for difficult shifts that require higher levels of control. However, during adulthood attention shifts become more automated (due to unquantifiable visual experience in a complex environment), requiring less frontal control. Instead, main differences between conditions can be explained by *occipital activation*. Only for more complicated shifts that involve an inhibition of prepotent responses (e.g. towards one of two targets or shifting while inhibiting saccades) the FEF pathway shows greater involvement. Therefore, the following ideas can be added to current models of infant development of attention:

1. Under 3 months attention is mainly subcortical and ERP responses are small and mainly contralateral (i.e. few interhemispheric connections)
2. In older infants frontal areas facilitate attention shifts. Additional involvement of the ipsilateral hemisphere enables effective attentional control. In addition, saccade-linked responses are more likely to overlap with disengagement responses, possibly amplifying the effect.
3. In adults attention shifts are more automated and mainly involve occipital areas. Only more difficult shifts, involving inhibition of eye-movements, require frontal involvement.

6.4.5 Relation to previous research on functional brain mechanisms of attention in infants

In line with findings on attention shifts in the gap paradigm (Csibra et al., 1998), a frontal positivity was observed in the current study. Additional testing of younger infants and the separate investigation of trials with sticky fixations provides further insights in the function of this response and prompts speculations about two different frontal mechanisms coinciding during attention shifts. An investigation of saccade-locked ERPs could shed more light on the questions whether a target-locked and a time-locked response overlap in this study, leading to the observed pattern. However, Csibra et al. (1998) did not find saccade-locked frontal responses preceding the saccade onset in 6 month old infants, suggesting that this method may not be successful in distinguishing different responses. Alternatively, source localisation or current dipole modelling could disentangle overlapping responses. This would be an interesting topic for future research.

Studies on sustained attention (Richards et al., 2010) suggest that the neural mechanisms, measured by the Nc component, become more localised and efficient with age. The localisation of responses seems to also play a crucial role in the current study. In particular, ipsilateral activation increases with age, coinciding with faster saccades under competition. This suggests that, although similar neural networks may be used throughout infancy, their effectiveness depends on the efficiency with which they respond to the correct location.

In line with previous literature, the current study confirms a crucial role of frontal areas in the development of attention shifts and adds that the lateralisation of responses may be crucial for the effectiveness of shifts.

6.4.6 Relation to previous research on structural brain mechanisms of attention in infants

Behavioural research on infants lacking one of their cerebral hemispheres after surgery shows that these infants have difficulties shifting attention to the side contralateral of the removed hemisphere under competition but not under non-competition conditions (Braddick et al., 1992). The current study found that cortical activation is present during attention shifts, confirming the idea that the cortex plays a role for them. However, both cortical hemispheres showed responses throughout infancy, with only the lateralisation changing with age in the age group tested here. Hemispherectomised infants are still able to shift towards the hemisphere ipsilateral to their removed hemisphere, but not towards the contralateral side under competition. However, in the current study the ipsilateral activation increased with age. If both hemispheres were required to shift under competition, shifts should be impaired in both directions after a hemispherectomy. On first sight the current findings contradict findings from the Braddick et al. (1992) study on hemispherectomy. However, these findings can be combined by considering an interactive specialisation approach. In typically developing young infants the contralateral hemisphere is still more involved than the ipsilateral one. Removing this more involved hemisphere may deprive them from the opportunity of building the interhemispheric connections that allow faster shifts. In line with a developmental specialisation approach, less interhemispheric activation may lead to less restructuring of the brain due to learning, preventing it from automatizing attention shifts as they are in adults. This would explain why re-fixations are generally slower in hemispherectomised infants, but not why there is a specific

impairment to shift towards the visual field contralateral to the removed cortex. Nevertheless, there are several reasons why different results might be found in hemispherectomised infants to this current study on typically developing young infants. Primarily, it is not possible for the infants in the hemispherectomy study to form inter-cortical connections at any stage in their development (before or after surgery), because from birth and in fact prenatally, they have one highly abnormal non-functioning hemisphere. However they have anatomically normal subcortical networks. This means that the connections between superior colliculus and the oculomotor nuclei may be functional and may underpin saccadic shifts under non-competition on the damaged side, and possibly on both sides. In summary, as an interaction of increase in connectivity and synaptic reinforcement in learning may be driving developmental improvement, elimination of interhemispheric connections during hemispherectomy may be interrupting typical development leading to difficulties in disengagement.

6.4.7 Combined eye tracking and EEG in infants

Eye tracking and EEG were combined in this study to measure brain mechanisms in infants. This combination has advantages and disadvantages for a young population that will be reviewed in this section.

There are several advantages to combining eye-tracking and EEG in infants. Firstly, the eye-tracker can be used to automate the beginning of trials, meaning that it is no longer necessary for an additional adult observer to watch infants during testing to judge whether they are fixating on the screen. This makes the method readily useable for single experimenters on their own, saving personnel and effort. The automation also saves time during trials, as the progress of the testing session does not depend on input from the experimenter, leading to shorter testing times and more trials completed in the short period for which infants are awake and attentive. In post hoc analyses the eye-tracking data can furthermore provide valuable insights on artefacts in the data. For example, the possibility of confounds of EEG data with eye-movements, which is a common problem in infants (DeBoer et al., 2007), can be minimised as an explanation for the data. Some infants do not tolerate electrodes around their eyes for this purpose (DeBoer et al., 2007), whereas a remote eye-tracker does not impair comfort and is therefore preferable. Thanks to the combinations of eye-tracking and EEG in this study it was possible to reliably exclude trials that were confounded with eye-movements to

improve data quality, which is one of the advantages of combining eye-tracking with EEG.

Unfortunately, there are also challenges to combining eye tracking and EEG in infant subjects. Data loss for combined eye-tracking and EEG is greater than for either of these methods on their own. Table 6.7 provides an overview of reasons for data loss. As in every infant study, some subjects will drop out due to inattention, fussiness or sleepiness (1), leading to drop outs or smaller trial numbers. As in all eye-tracking studies, the eye-tracker can lose the signal during testing (2) (review: Aslin & McMurray, 2004; Gredebäck et al., 2009), leading to longer testing times, resulting in less successful trials before the infant becomes inattentive. Post-hoc analyses can identify additional noisy eye-tracking data, meaning that trials need to be excluded (3) (e.g. de Urabain, Johnson, & Smith, 2014). However, in addition to eye-tracking data loss, the EEG data may also contain noise in some trials (Luck, 2005; Regan, 1989), often other trials than the noisy eye-tracking trials, resulting in a further decrease of trial numbers (4). As eye movements are an inherent part of trials and can cause artefacts (Gratton, 1998; Jervis, Ifeachor, & Allen, 1988; Joyce et al., 2004), some of them may occur within the extracted time window, meaning that these trials with early eye movements also need to be excluded (5). After all of these possibilities of losing data, it is quite likely that several infants will not fulfil criteria for the minimum number of trials per condition to average across to receive a reliable EEG signal, without distortions due to noise, leading to whole data sets of infants being excluded (6). The current study had a dropout rate comparable to previous infant research (e.g. Csibra et al., 1998; Csibra et al., 2000; de Haan & Nelson, 1997); however, the combination of eye tracking and EEG made it difficult to obtain a sufficient trial number due to more possibilities of data loss. A comparison of the infants that needed to be excluded because they did not reach the minimum number of trials compared to the infants included in the analysis, showed that both groups did not significantly differ in saccade latency or proportion of sticky fixations, suggesting that the strict inclusion criteria did not bias the sample in regards to the behavioural outcome measures. However, infants' individual EEG noise thresholds as indicators of data quality (M = 39.4 µV, SD = 20.2 µV, section 6.3.1) were considerably higher than adults' individual thresholds (M = 13.7 µV, SD = 3.94 µV, see Chapter 5, section 5.3.1), t = 6.479, p < .001, which is in line with previous research on infant brain responses being significantly noisier than the adult responses (Brown, 1994; Picton & Taylor, 2007). This is visible in the wave plots

displayed in *Figure 6.6* and *Figure 6.11* above, which show greater noise than adult plots (e.g. Figure 5.6 in Chapter 5). To minimise noise, stricter filter cut offs were used in infants (0.1 Hz high-pass filter instead of 0.01 Hz, see Chapter 2, section 2.3). However, the option of decreasing noise through filtering was limited for this combined measure of eye tracking and EEG, as regular eye movements would cause filter artefacts if too strong filters were used (see discussion in Appendix C). The next chapter (Chapter 7, section 7.2.2) discusses adjustments that were developed throughout the thesis to improve data quality in infants and adults.

Table 6.7. *Reasons for data loss when combining eye-tracking and EEG in infants.*

1	Non-compliance of the infant during testing (9 infants excluded = 11.3%)
2	Signal loss of the eye-tracker during testing*
3	Noise in eye-tracking data determined during post-hoc analysis (8.6% of trials)
4	General noise in EEG data determined during post-hoc analysis (15.0% of trials)
5	Eye movement artefacts in EEG data due to extraordinarily short saccade latencies (2.4% of trials)
6	Loss of whole subject data sets because they did not fulfil the minimum criteria for inclusion (42 infants excluded = 52.5%)

**Signal loss during testing results in the eye tracker taking longer to register a fixation on the stimuli and therefore to automatically initiate trials, meaning that fewer trials can be completed before the infants becomes tired (depending on the individual infant's state).*

Different methods can be used to investigate changes in the quantified voltage over time. The current study examined the potential changes immediately after a distinct stimulus onset event, so-called *transient event-related potentials* (tERPs). As the interval between stimuli is long enough for the brain response to be completed before the next stimulus, the brain is in a "resting state" before the occurrence of the stimulus (Regan, 1977). In contrast, in the method of *steady-state visually evoked potentials* (SSVEPs), the same stimulus is flashed at the subject repeatedly at a high frequency, so that the brain's response becomes a periodic rhythm (Regan, 1989). The SSVEP towards the flickering stimulus follows the same fundamental frequency as the initiating stimulus and can be extracted using Fourier analysis. As the gaps between stimulus presentations are short, the brain does not return to its resting state between stimuli

(Regan, 1989). Due to repetitive stimulation more data can be recorded in a shorter time with a better-signal to noise ratio (Regan, 1977). It therefore provides a quicker way to record evoked potentials and could be used for future studies on attention development. A combination of the current methodology with steady-state ERP measures may improve the signal to noise ratio in data of young infants.

6.4.8 Diagnostic use

Results of the current study show that an increase in ipsilateral frontal activation might reflect a developmental milestone. Further research is required to replicate this finding and monitor exact changes with age. If this effect proves to be a developmental milestone, it would be interesting to use it for diagnosis of atypical development. As reviewed above, combined eye tracking and EEG leads to low data quality, making it difficult to observe effects on an individual level. The paradigm could be altered to include fewer conditions, to have a higher signal to noise ratio. In infants the signal to noise ratio is higher than in adults (DeBoer et al., 2007; McCulloch, 2007), which might make it possible to use ERPs as an individual measure rather than group data despite low trial numbers. However, the noise level of the current EEG data and the reliability of the effects found for saccade latency (as seen in replications of previous research and of studies within this thesis) suggest that eye-tracking measures may be a more applicable diagnostic tool on an individual subject level. This is because less eye tracking data is lost due to noise than EEG data, because only the eye tracker needs to receive a clean signal, whereas for a successful EEG data trial, both the eye tracker and the EEG system need to show a clean signal.

6.4.9 Summary and conclusion

The current chapter aimed at investigating the development of neural mechanisms of attention shifts during infancy by combining eye-tracking and EEG in infants between 1 and 8 months of age. Although both methods could successfully be combined and findings were in line with previous research, the data loss was high and behavioural measures were less prone to noise than neural measures. The results replicate behavioural findings from Chapter 3, showing an improving ability to shift attention under competition with age. On a neural level, this change coincided with changes in the lateralisation of a frontal positivity. This study confirms the involvement of frontal areas in attention shifts in infants, as suggested by neurodevelopmental

models. It furthermore shows that the efficiency of the lateralisation plays a crucial role for developmental improvements in the ability to shift attention. The next chapter will relate infant findings to adult results from the previous chapters and derive conclusions.

Chapter 7 Discussion

7.1 Summary of previous chapters

This thesis investigated the development of cortical mechanisms of attention using combined eye-tracking and EEG. In the first part (Chapters 2 to 4), this novel methodology was developed, tested on infant and adult populations, the reliability was determined and it was linked to previous research. In the second part (Chapters 5 to 6), the method was used to investigate developments in the ability to disengage and shift attention with age.

Chapter 1 reviewed the current literature on attention. It showed that the Fixation Shift Paradigm is an established method to non-verbally measure attention development in infants. Behavioural research and lesion studies prompt speculations about cortical control as a necessity to control attention shifts that involve disengagement. However, it was established that direct measures of brain responses during overt attention shifts are rare as is direct research on neural mechanisms of attention development.

Chapter 2 described the development of a new non-verbal method to measure brain responses during overt attention shifts by combining eye tracking and EEG. It critically discussed the challenges of this method due to timing arrangements of both pieces of hardware (see Appendix D) and dealing with EEG artefacts due to regular eye movements (see Appendix C). After considering caveats, a novel measure of neural mechanisms of attention shifts was developed as a basis for studying cortical mechanisms of visual attention.

Chapter 3 developed and tested a programme to automatize the commonly used Fixation Shift Paradigm by combining the behavioural task with eye tracking. The new eye-tracking method was tested in infants between 1 and 8 months, replicating previous findings from the purely behavioural paradigm. This established that the automated approach can be used as a fast test of attention for non-verbal populations from an early age. The approach has higher temporal accuracy than trained adult observers and data on fixation positions can be directly fed back into the experimental programme during testing, making it possible to use this information in combination with other methods, like EEG.

Chapter 4 combined eye-tracking and EEG to simultaneously record saccades and brain responses in adults. As most previous studies instructed their participants to covertly shift their attention to stimuli while inhibiting eye-movement, this chapter

aimed to create a bridge between previous covert attention studies and the overt attention shifts measured in this thesis. Adult subjects completed an identical fixation shift task during which they either had to manually respond to a peripheral target while maintaining central fixation (covert shift) or make a saccade towards a peripheral stimulus (overt shift). Results show that overall responses are similar for covert and overt shifts of attention, including occipital positivities and frontal negativities. The main difference is a frontal positivity that only occurred during covert attention shifts and during double target trials, possibly reflecting the inhibition of saccades towards one or several targets. The successful extraction of ERP components in the overt attention task indicates that a combination of eye-tracking and EEG is possible and allows removing eye-artefacts from the EEG data. It can therefore be used as a tool for studying attention shifts in nonverbal populations.

Chapter 5 combined the Fixation Shift Paradigm with eye-tracking and EEG to study differences of shifts involving disengagement compared to no disengagement in adults. The results replicate findings from Chapter 4, showing occipital positivities and frontal negativities involved in attention shifts. Already early responses before saccade onset differed between conditions. An occipital positivity showed significantly shorter latencies under non-competition than under competition conditions, reflecting the same time-course as behavioural findings. In line with previous models suggesting connections from visual areas to superior colliculus (SC), the earlier posterior activation in non-competition conditions may allow SC neurons to reach a saccade execution threshold earlier, resulting in faster saccade latencies. To investigate to what extent differences between conditions are caused by the offset of the central stimulus, a second study was conducted to subtract the offset response from the raw wave. It showed that responses are partially connected to an offset response, suggesting that the offset of a visual stimulus can facilitate attention shifts.

Chapter 6 used the newly established method combining the FSP with eye-tracking and EEG to test infants between 1 and 8 months of age. The pattern of longer saccade latencies under competition that decrease with age as found in Chapter 3 was replicated. Brain responses during attention shifts involved a frontal positivity and a posterior negativity in all age groups. The number of response components and response amplitudes increased with age. The frontal response changed lateralisation with age, being greater in the contralateral hemisphere in young infants and greater in the ipsilateral hemisphere in older infants. Frontal responses were significantly smaller in trials when infants failed to shift attention, suggesting that the frontal responses are

crucial for attention shifts. In line with previous models, the frontal response may reflect top-down connections from frontal eye fields regulating attentional control. The change in lateralisation with age suggests that the efficiency of the response, reflected in the precise lateralisation of brain responses in relation to the target position, plays a greater role for developmental changes than the overall response amplitude.

The current chapter links findings from different chapters that were summarised above. It discusses the method development and its applications, brings together findings of this thesis, relates development during infancy with neural mechanisms in adults and refers the findings of this thesis to current literature. It ends with future directions for research and an overall conclusion.

7.2 Methodology: Critical discussion

7.2.1 Advantages of the method

The first aim of this thesis was to develop a new method for simultaneously measuring eye movements and their underlying brain responses by combining eye tracking and EEG. As reviewed throughout this thesis, the combination has several advantages; in summary:

1. It can be used with non-verbal populations
2. The eye tracking data can be accessed online during testing, making it possible to react to the subjects fixation position. This has several advantages, for example it can be ensured that subjects fixate on the centre of the screen when a trial is started, it can be ensured that the distance between the subjects' fixation position and appearing stimuli is set at a constant criterion and it is possible to automatically show attention-grabbing stimuli (e.g. Teletubbies movies) when subjects' gaze is not on the screen.
3. The method is automated, meaning that no manual input from the experimenter about fixation judgements is required, making the procedure faster and less prone to human error.
4. Eye tracking data and EEG data can complement each other, for example the eye tracking data can be used to exclude trials that contain eye movement artefacts.

However, despite the advantages there are several challenges and disadvantages that need to be carefully considered when combining eye tracking and EEG and will be reviewed in the following section and solutions will be discussed.

7.2.2 Data quality: challenges and solutions

Data loss occurs more readily when using combined eye tracking and EEG. With specific methods some but not all data loss possibilities can be minimised, and the methods that were used to successfully improve data quality will be reviewed in this section. Table 6.6 in Chapter 6 summarised the different ways in which data can be lost. The following section will discuss how these challenges can be (partially) overcome.

1. Infants commonly become non-compliant during testing because they get tired or hungry. In this thesis this problem was solved by allocating fairly long time windows for testing, letting the infant sleep and feed whenever necessary and waiting until the infant was in a happy and alert state for testing. This sometimes made it necessary to wait for more than an hour to complete a testing session of 10 minutes. This is time consuming but can increase data quality as can be seen from the fact that only a small number of infants were excluded due to fussiness.

2. The eye tracker can lose signal during testing (review: Aslin & McMurray, 2004; Gredebäck et al., 2009), meaning that trials are not automatically initiated because fixation criteria for trial onset are not fulfilled. Signal loss was minimised in this thesis by (a) adjusting lighting conditions to improve signal strength (b) mounting neutral density filter sheets in front of the eye tracker's sensors to modulate the intensity of the measured reflection and (c) adjusting the position of the subject to let the eye tracker slightly "undershoot" their eyes to maximise signal strength. These three methods can minimise but not entirely prevent signal loss.

3. Some trials need to be excluded due to bad eye tracking data quality. The three previously stated methods for avoiding signal loss can decrease the number of trials to be excluded post hoc as well.

4. Additional trials may be excluded due to noise and artefacts in the EEG data (e.g. Luck, 2005; Regan, 1989). Adults can be instructed to remain as still as possibly during testing to avoid these artefacts. However, infants commonly move during trials leading to additional noise. Some noise sources can be decreased by instructing the person

holding the infant during testing to remain still to avoid motion artefacts caused by their movements. Furthermore, a median threshold procedure (see Chapter 2, section 2.3) was used on individual subject data to fit the criteria as efficiently as possible to individual data, ensuring that the threshold was not set too strict which would result in unnecessary exclusion of some clean data.

5. Eye movements, which are an inherent part of all trials in this thesis, can create additional artefacts in EEG data (e.g. Gratton, 1998; Jervis et al., 1988; Joyce et al., 2004). In particular, care must be taken when determining high-pass filter settings that can lead to distortions of the data as demonstrated in Appendix C. Four actions were taken to minimise artefacts due to eye movements: (a) only a short time window of EEG data after stimulus onset was extracted to avoid eye movements overlapping with the extracted time window leading to artefacts; (b) eye tracking data was used to exclude trials with early saccades to ensure that no outliers fell within the extracted time window; (c) no online high-pass filters were used during data recording to avoid distortions of the data and (d) the post hoc high pass filters were set to a low criterion of 0.01Hz for adults and 0.1 Hz for infants, which has been shown not to induce filter artefacts (Appendix C) to avoid distortions.

6. All above mentioned criteria can lead to trial exclusion, possibly to the extent that some subjects' data sets cannot be included in the analysis because the minimum data criteria were not fulfilled. The number of excluded trials can be minimised but data loss cannot be entirely avoided. Adult subjects can be asked to complete higher trial numbers and due to the high trial numbers used in adult studies for this thesis, subjects did not need to be excluded because of insufficient trial numbers. However, infants are only attentive for a shorter period of time, making it impossible to increase trial numbers. Therefore, the number of conditions should be kept to a minimum to increase the number of trials within each condition. In this thesis infants completed the same conditions as adults to increase comparability of subject groups. However, future research should consider using fewer conditions to maximise the number of trials per condition.

In summary, data loss is a greater problem for combined eye tracking and EEG than for either of these methods on their own. Different methods reviewed above can minimise data loss to a certain extent; however it is important to consider data quality carefully when combining eye tracking and EEG.

7.2.3 Timing eye tracking and EEG

To combine eye tracking and EEG the timing of both methods needs to be carefully investigated to ensure a correct alignment of both data sets. EEG data delays due to amplifiers are a common problem in some EEG systems (e.g. Electrical Geodesics, 2014) and can lead to wrong conclusions about ERP latencies. Guidelines published by manufacturers are often incorrect and need to be revised (e.g. Electrical Geodesics, 2014), suggesting that it is recommendable to test the timing of a specific set up independently of the manufacturer. Appendix D developed a simple method for testing the timing of an EEG set up that can be used with different EEG systems. I recommend using such a test for every EEG study to ensure correct timing of ERPs.

Similar to EEG systems, eye-trackers can also process data with a delay, making it difficult to align EEG and eye-tracking data. Appendix D showed that the delay of an EEG system can be measured with a simple and accurate method; however, it is more difficult to measure the exact timing of saccades. In this thesis the exact delay of the eye-tracking data was not crucial for the experiment, as it was used to determine fixations on-line, while saccade latencies were calculated offline and therefore less critical for timing. Guidelines published by the manufacturer were therefore used to calculate the maximum delay, ensuring to use the strictest criterion. If more temporal accuracy is required online, one possibility would be to use EEG data excursions to determine the exact timing delay of eye-tracking data and account for it. *In conclusion, both EEG and eye tracking should be checked for temporal accuracy.*

7.2.4 Limitations of the method

Combined eye tracking and EEG can be used to monitor brain responses during overt attention shifts with a high temporal accuracy. At the sampling rate of 250 Hz used throughout this thesis, changes in neural responses can be detected within 4 ms, providing a high temporal precision. However, EEG has a rather low spatial resolution compared to other neuroimaging methods, making it difficult to determine sources of the responses observed at the surface of the scalp. As the results from Chapter 6 suggest that two frontal components may overlap to form the observed response, it would be interesting to get further insights to the spatial localisation of response sources.

Two methods to simultaneously collect structural and functional information about the brain are functional MRI (fMRI) and source localisation with high-density EEG arrays. There have been attempts of conducting fMRI on infants, specifically using visual stimulation through closed eyelids during sleep (Born et al., 1998). However, in order to investigate attention shifts infants need to be awake. MRI in awake infants is very time-consuming, as they need to be in a happy and alert state for testing, and it is less feasible for this kind of paradigm that involves eye-movements, as they cause artefacts in the fMRI data (e.g. Chen & Zhu, 1997). In summary, the usability of fMRI for research similar to the studies conducted in this thesis is debatable. In contrast, the high density EEG system used in this thesis (Tucker, 1993) has successfully been used for source analysis in adults, young children and infants (e.g. Bathelt, O'Reilly, Clayden, Cross, & de Haan, 2013; Bathelt, O'Reilly, & de Haan, 2014; G. D. Reynolds & Richards, 2005; Thomas & Casey, 2003). However, source analysis should only be conducted on data with low noise levels (Picton et al., 2000), making this method challenging for use in young infants. Due to great changes in the brain and skull structure with age, its suitability for infants has been debated (DeBoer et al., 2007; M. H. Johnson et al., 2001). Furthermore, source localisation refers from a two-dimensionally measured signal (scalp response) to a three dimensional space (areas in the brain). Therefore, several different sources could account for one signal detected at the surface, known as the inverse problem (review: Grech et al., 2008; Pascual-Marqui, 1999). Additional structural MRI recordings on the same subjects also tested with EEG can facilitate source localisation by considering anatomical specificities of each subject (e.g. Phillips, Rugg, & Friston, 2002; G. D. Reynolds & Richards, 2009; Thomas & Casey, 2003).

To obtain more information about the cortical sources of responses observed in this study, in future studies infants could complete an additional structural MRI session to obtain more information about their neural structure and to establish a template for source localisation of responses. I piloted the idea of using MRI combined with the FSP on children between 6 and 10 years of age, who completed a touch-screen version of the paradigm and an additional MRI session with diffusion tensor imaging (DTI) to monitor the structure of their neural connections (this study is described in Appendix M). The study conducted in Appendix M tested children, instead of infants, in an MRI scanner, as they are more compliant participants. However, DTI can also be sampled during sleep in infants, making it a suitable method for structural development (see e.g. de

Haan, 2007a; Jerger, Martin, & McColl, 2004). Structural brain measures derived from DTI can then be related to attentional development to provide further insight into structural correlates of the observed neural potentials. As the current thesis prompts ideas about interhemispheric connections playing a crucial role for the developing ability to shift attention, DTI could be used to directly investigate these connections and relate them to the observed lateralisation of ERPs. In future EEG could be combined with MRI to relate the functional findings to structural development.

The current thesis focused on ERPs after target onset to monitor the process starting from target appearance over disengagement from the central stimulus location to a shift towards the peripheral target and an engagement with it. It would also be interesting to extract the ERP data locked to the saccade onset. This was for example done in older infants (Csibra et al., 1998; Csibra et al., 2000) and adults (Csibra et al., 1997). Locking the ERPs to stimulus onset shows how the potential changes in relation to the stimulus onset and how activation changes in different areas resulting from the stimulus onset. However, some components might be more related to the initiation of the saccade than the stimulus onset (although they might be somewhat driven by the stimulus onset). One example of this is the spike potential that occurs shortly before saccade onset and can provide some information about disengagement (Csibra et al., 1997; Csibra et al., 1998; Csibra et al., 2000). The current thesis focused on stimulus-related potentials, as previous research did not find the saccade-locked responses, that are usually observed in adults, in young infants (Csibra et al., 1998). To find out which components are more related to the stimulus onset and which are more related to saccade planning, one could extract both the ERPs locked to the saccade onset and to the stimulus onset. This can be done by detecting large potential shifts in EEG data suggesting that an eye movement occurred and linking the potentials to them (for a detailed description of the method see Csibra et al., 1997; Csibra et al., 1998; Csibra et al., 2000). In theory, eye tracking information could also be used to detect saccades and extract ERPs preceding them. However, as discussed above, the timing of eye trackers is not very accurate and needs to be carefully aligned with EEG data to ensure correct timing of both signals. To avoid misalignments it would be more temporally accurate to use saccades detected by EEG for saccade-linked ERP extraction. Table 7.1 summarises the overall advantages and disadvantages of using combined EEG and eye tracking to monitor attention development.

Table 7.1. *Advantages and disadvantages of the methodology developed during this thesis for investigating neural development of attention.*

Advantages	**Disadvantages**
High temporal accuracy of eye tracking and EEG	EEG has a fairly low spatial resolution
Simultaneous recording of eye movements and brain responses	Eye movements can create artefacts in the EEG data
On-line access to eye tracking data allows for control of stimulus presentation	Synchronisation and timing of eye tracking and EEG data needs careful consideration
The method can provide valuable insights to development on a group basis	Currently not suitable for individual diagnostics in infants
Eye tracking can be used to identify noisy EEG trials	Both methods can lead to data loss due to noise, increasing the probability of losing trials
Opportunity to test non-verbal populations	
Automatized approach saves time and personnel	

7.2.5 Differences in infant and adult methods

To identify functionally similar components in adults and infants, subjects should be tested with the same paradigm to identify components that vary with the different conditions of the paradigm (de Haan, 2007a). In the current thesis both infants and adults completed an identical paradigm, using an identical testing set up. This was done to ensure a maximum comparability of both subject groups. However, the overall neural patterns differed between infants and adults.

Saccade latencies were analysed using the same algorithms to minimise differences. However, due to data quality differences, several specifics of the EEG data needed to be processed differently. Firstly, high pass filter settings were higher in infants than in adults (0.1 compared to 0.01 Hz), to reduce the slow drift due to motion artefacts in young infants, which is commonly described in the literature (e.g. Hoehl & Wahl, 2012; Luck, 2005). Secondly, due to high trial numbers in individual adult subjects, it was possible to analyse peak amplitudes and latencies. However, these methods are easily affected by high frequency noise and sudden peaks (Luck, 2005; Regan, 1989) and

therefore not suitable for infant data. Instead, mean amplitudes were calculated in the younger subjects. Although both measures quantify the same underlying outcome (ERP amplitude), they cannot directly be compared. Thirdly, adults were instructed to look at upcoming targets, giving them an opportunity to prepare to react. Possibly, adults were more actively preparing to look at new things (i.e. activation already before target onset), while infants simply reacted to what was happening. This may have influenced cognitive processes during attention shifts. Another difference was that infants were shown short cartoons between trials to keep them engaged in the task. This may be considered as a reward in response to a shift, conditioning them to shift more quickly. On the other hand, it is quite likely that adult subjects (mainly students) were also interested in shifting as quickly as possible, to finish the experiment faster. In summary, some processes differed between infants and adults, suggesting that they should not be directly statistically compared. However, a qualitative comparison can provide valuable insights into common principles tested with the identical task and will be described below.

7.2.6 Applications

The method of combined eye tracking and EEG has been successfully used in verbal and nonverbal populations in this thesis and may find applications in different other areas as well. The current thesis used a well-established attention paradigm to create a template of neural mechanisms during shifts that are commonly measured in a laboratory context. It is possible to use eye trackers in real life situations due to their high spatiotemporal accuracy (e.g. Falck-Ytter et al., 2013). The current combination of eye tracking and EEG could also be transferred to a more natural context. Nowadays portable eye trackers can be used in everyday life. They can be used to simultaneously film the visual field of subjects and monitor their eye gaze (video-coding eye-tracking systems). This would make it possible to use combined eye tracking and EEG to investigate attention shifts in natural real world scenes. Data from the eye tracker can be used to determine when a subject shifted gaze from one object to another (e.g. from the parent's face towards a toy) and determine what brain activity occurred before the shift (*Figure 7.1*).

As reviewed above (section 7.2.3), it is crucial to ensure an accurate temporal alignment of eye tracking and EEG data. Therefore, to apply the current method to a real world context it would be desirable to collect eye tracking and EEG data at the

same sampling rate, which is possible with high frequency eye trackers (e.g. EyeLink1000: SR Research Ltd., 2008). Furthermore, exact timing measures of the systems need to be taken (Appendix D). After these additions to the original method it would be possible to apply combined eye tracking and EEG to study attentional disengagement in a real world context.

Figure 7.1. Application of the method to a realistic context. In a real-world situation, eye tracking could be used to determine a subject's fixation position (e.g. traffic light, left), while cameras detect changes in the visual scene (e.g. car appearing, middle) and send triggers to the EEG system, which can then measure neural potentials between the appearance of a new target and a shift towards it (right).

Additional applications of the overall method are numerous. It is possible to use the method for different subject groups with verbal impairments (e.g. people with autism or language impairments) to provide an attention measure that is fair to all subject groups. The method is equally suitable for infants who cannot communicate verbally as for adults who suffer from language impairments after strokes. For all of these populations the method developed throughout this thesis can be used to investigate neural mechanisms of attention.

The method can also be transferred to other subject areas to nonverbally study brain responses. For example, in the areas of face processing the neural responses to different facial features may be studied by extracting which facial feature subjects fixate on and comparing neural responses between them. In social research it can be investigated which agents subjects look at and whether neural responses may show preferences for friendly compared to unfriendly agents. In summary, the method can be applied to various different areas of research.

7.2.7 Clinical implications

The current thesis investigated neural attention mechanisms in typically developing subjects to provide a baseline of typical attention development. However, it is well established that the Fixation Shift Paradigm can be used to diagnose subjects with attention impairments who significantly differ from typical populations (Atkinson & Braddick, 2011, 2012). Studying brain responses in typically and atypically developing infants in the same task can provide insights to differences in neural mechanisms (M. H. Johnson et al., 2005). Studying populations with attention impairments, for example premature infants (Atkinson & Braddick, 2007, 2012) could therefore provide information about atypical neural mechanisms. Pilot results of eye tracking in the FSP can be found in Appendix N. They show that mildly premature infants show significantly longer saccadic latencies than their term-born peers despite a small sample size (see Figure N.3 in Appendix N). These results suggest that an automated FSP with eye tracking can be used as a diagnostic tool for atypical attention development from an early age on in risk groups like premature infants (for the full study see Appendix N). Further follow up research on a greater group of premature infants could provide charts of typical and atypical development that may allow early diagnosis and intervention for at-risk infants.

In addition to the above mentioned behavioural comparison of typical and atypical development, abnormal development of neural responses would also be an interesting topic for future studies. Chapter 6 investigated typical brain mechanisms in infants. It would be intriguing to use EEG in atypically developing infants to determine the brain mechanisms that underlie dysfunctional development. On a group basis this could provide insights to the mechanisms that need to develop to allow infants to shift attention. Although these findings would have interesting implications on a group level, it is unlikely that ERPs in the FSP can be used on an individual basis. As discussed in section 7.2.2, a high number of trials need to be collected from each infant to get a sufficient number of noise-free trials to average the EEG signal across. This high number is often not reached on an individual level, leading to noisy signals. As findings rely on group rather than individual data they cannot be used to infer to individual infants, which is a common problem with infant ERPs (Coch & Gullick, 2011). EEG in the FSP is therefore currently not suitable as an individual diagnostic tool.

In summary, the combined EEG and eye tracking method can be used to investigate neural differences between groups that are developing typically or atypically, while diagnostic on an individual basis can only reliably be investigated with eye tracking at the current state of technology.

7.2.8 Summary: Methodology

The first aim of this thesis was to develop a method to investigate brain responses during overt shifts of attention. The discussion above shows that the combination of eye tracking and EEG was successfully developed and used throughout this thesis and can be a useful tool for studying brain responses on a group basis, but at the current state of technology not on an individual basis. The method can be transferred and applied to various different areas.

7.3 Brain mechanisms of attention development

The second aim of this thesis was to investigate the neural mechanisms of attention development in infants and adults to investigate current theoretical models of development with direct measures of brain activity. The current section will first compare findings from infants and adults and then apply them to current models of attention.

7.3.1 Comparison of adult and infant findings

This thesis aimed at investigating neural mechanism of attention shifts in adults and during development in infancy. On a behavioural level, infants and adults showed the typical pattern of longer latencies in competition than in non-competition conditions that decreased with age. However, the neural mechanisms involved in attention shifts seemed to differ in infants and adults. In adults, the main difference between competition and non-competition was found in posterior regions. Their early occipital positivities showed significantly shorter latencies in non-competition than in competition conditions, reflecting the pattern of saccade latencies. Furthermore, the posterior positivity peaked in contralateral areas first, followed by a greater ipsilateral response. Adults only showed frontal positivities in conditions that involved inhibition of eye movements, including double target conditions (inhibition of eye movements towards one of the two targets) and covert attention shifts (inhibition of overall eye movements). However, infant subjects showed a different response pattern, including a

bilateral frontal positivity coinciding with a posterior negativity. The lateralisation of the frontal response changed during infancy. Contralateral response amplitudes decreased with age, while ipsilateral amplitudes increased. During sticky fixations, a failure to shift attention, infants showed smaller frontal response than during correct re-fixations.

In summary, the main difference between infant and adult subjects are that a frontal positivity is always visible during attention shifts in infants, while it only occurs for more complex attention shifts involving additional saccade inhibition in adults. In contrast, the occipital cortex seems to play a more crucial role for attention shifts in adult subjects than in infants. In the following, the observed neural differences between infants and adults will be discussed in regards to previous neural models and new additions to them.

7.3.2 Integration of adult and infant findings in regards to models

Neurodevelopmental models suggest that attention is mainly subcortical in the first 2 months of life, with cortical control emerging from 2 months onwards, starting with an occipital pathway that can activate the superior colliculus (SC) through posterior visual areas, followed by a frontal attention pathway that leads to additional attentional control through FEF (Atkinson, 1984; Bronson, 1974; M. H. Johnson, 1990). This thesis provides evidence for occipital and frontal responses during attention shifts in all age groups of infants and adults. On the one hand, this supports the idea that these areas are crucial parts of attentional brain networks. On the other hand there is no direct support for a sudden onset of the involvement of specific neural areas with age. On contrary, both frontal and occipital areas showed responses in the youngest age group (1.5 to 2.5 months) already, although responses were weaker. In the following I will discuss how the findings relate to the different pathways of neurodevelopmental attention models.

The frontal cortex has widely been suggested as a crucial area for attentional control (Atkinson, 1984; Crowne, 1983; M. H. Johnson, 1990; Kimchi, 2009; Neggers et al., 2005; Schiller, 1985). In the current thesis, infant subjects indeed showed a frontal positivity that consistently occurred during attention shifts. The overall frontal activation did not change with age; however, the lateralisation did, showing a decrease in contralateral and an increase in ipsilateral areas. Furthermore, frontal areas were less

active during sticky fixations, which reflect a failure of the system to shift attention. Taken together, this evidence somewhat supports developmental models (e.g. Atkinson, 1984; M. H. Johnson, 1990), suggesting that a frontal pathway (possibly through FEF) is involved in attentional control in infants. However, adults did not show the frontal positivity observed in infants during simple fixation shifts.

As adults have more experience with the visual world and more practice in shifting attention, their mechanisms during simple attention shifts may be more automatized and therefore do not require frontal control. This explanation is in line with the finding that a positive activation occurred during more difficult shifts involving saccade inhibition (Chapter 4 and 5). As everyday behaviour rarely requires adults to inhibit saccades, they have less experience with these attention shifts, require additional control and therefore show additional frontal activation. In particular, frontal activity may reflect controlled inhibition of eye movements. To further investigate this idea, it may be interesting to test adults who have everyday practice in covertly shifting attention (e.g. pantomimes, poker players) to see if they show more automation of these shifts (*Figure 7.2*). Ipsilateral frontal activation increases with age during infancy and may reflect an increasing inhibition of eye movements to the wrong direction, facilitating correct responses. *In summary, the frontal pathway seems to play a crucial role in infants. However, in adults the occipital cortex shows more consistent differences between non-competition and competition conditions.*

Neurodevelopmental models suggest a direct connection from occipital areas to SC. In adults, this pathway may be the crucial one for simple attention shifts. It may reflect a simpler mechanism (only posterior responses are required, no additional frontal control) that allows faster saccade initiation, leading to faster saccades in adults than in infants. Schiller (1985) prompted the idea that different attention pathways may conduct at different paces, suggesting that the latency of a saccade depends on the velocity of the neural pathway that was involved in creating it. In line with this idea, it is possible that the frontal pathway mainly used in infants elicits saccades more slowly than the more automated occipital pathway mainly used in adults.

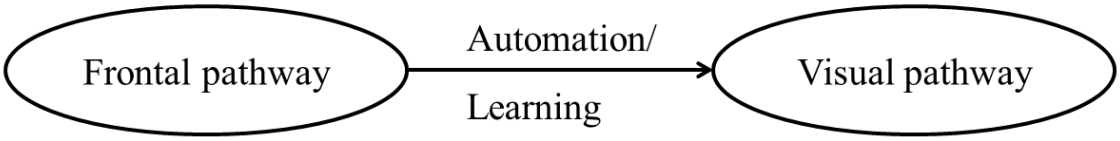


Figure 7.2. Change in predominant attention pathways with age. Frontal activation in infants suggests that a frontal pathway is involved in attention at a young age, while learning and automation lead to a fast visual pathway to be involved in attention shifts in adults.

Adding on to neurodevelopmental models, the current results provide evidence for a frontal and an occipital pathway. However, they suggest that both pathways do not need to be involved simultaneously to succeed in shifting attention. Instead, the frontal pathway is only required for shifts that are demanding in regards to the current skill level of the subject, while simple attention shifts can be controlled by the occipital pathway only.

7.3.4 Developmental accounts: maturation vs interactive specialisation

Different brain areas were most prominent during attention shifts in infants and adults, suggesting that the overall brain networks involved in infants and adults differ. This section will discuss which developmental views can account for these findings (see Table 7.2 for a summary). A modulatory view would have suggested that specific neural attention modules become active with age. For example it would state that the frontal cortex does not become functional until a certain age. Findings from this thesis do not support the modulatory view. In contrast, the frontal cortex is involved in attention shifts from the earliest age group (1.5 months) onwards and it is only the activation within the frontal cortex that changes in lateralisation. Therefore, the current thesis provides opposing evidence to theories stating that specific modules simply become active with age. Instead, I suggest that the efficiency with which these areas are used plays a crucial role for developmental improvements in the age range tested here.

Developmental research in different areas has suggested that the same behavioural functions can coincide with activation in different neural networks in different age groups. For example, lesion studies show that different area lesions lead to different impairments at different ages (Bates et al., 1999; Malkova et al., 2000). Therefore, a possible explanation for different neural findings in infants and adults may

be that the overall attention networks differ between infants and adults. A frontal attention network may be involved in attention shifts in infants, while an occipital attention network becomes involved in adults. However, a frontal positivity was still visible in adult subjects; yet, only when the task demanded additional control, for example an inhibition of saccades, suggesting some use of a frontal network in adults. These findings suggest that similar networks are involved in attention shifts, but different parts of the networks are used more intensely at different ages.

"*Interactive specialisation*" (IS) describes a more complex idea, suggesting that experience interacts with brain development. This approach has been put forward in the area of face processing development, as intrinsic primitive (possibly subcortical) modules may guide infants to attend to relevant facial features, which leads to increasing visual experience with these features, which as an extrinsic factor further shapes the brain areas responsible for face processing (de Haan et al., 2002). M. H. Johnson (2001) suggests that the adult brain is more specialised than the infant brain with specific areas being responsible for different behavioural functions. In line with this theory, de Haan et al. (2002) demonstrated that neural mechanisms of face processing are more widely distributed in infants than in adults, leading to less specialisation and more plasticity. Also for the overall social brain network, similar brain regions have been found to be involved in infants as in adults, suggesting that the same social brain network may be involved, but less specialised or less efficient in infants (M. H. Johnson et al., 2005). The current thesis focused on the development of visual attention, and similarly showed, that frontal activation was widespread in infants with increasing lateralisation with age. This means that neurodevelopmental changes do not include simple additions of new brain areas or modules, but changes in connectivity across different regions. This is in line with the idea of developmental specialisation (de Haan et al., 2002; M. H. Johnson, 2000), as results showed no simple additions of specific activity, but frontal areas were found to be active in all infants and only the connectivity between hemispheres, measured as lateralisation, changed with age.

Furthermore, the interactive specialisation approach suggests that learning can affect the brain, leading to reorganisation of cortical connections or a redistribution of tasks to different brain areas than the ones previously used (M. H. Johnson, 2000). In Chapter 4 and 5, adult subjects mainly showed occipital responses involved in attention shifts compared to frontal and occipital responses in infants. In line with the IS

approach, constant learning in adults may lead to an automation of attention shifts, resulting in reallocation of brain structures involved in attention shifts.

Most views suggest that frontal areas are the last to develop (similar to a modulatory view), as synaptogenesis of these areas takes longer. However, M. H. Johnson (2000) suggests that the frontal cortex shows specialisation earlier than other cortical areas because it can control many other areas through numerous feedback connections and therefore is crucial for general control of behaviour. The current thesis shows that specialisation effects in frontal areas can be clearly seen to develop between 2 and 8 months of age. These findings suggest that it is possible that frontal areas become involved from an early age on, as suggested by M. H. Johnson (2000). However, their specificity still develops with age, as shown by increased synapse growth, allowing more efficient and faster control in adults than in infants.

Table 7.2. *Relation of different approaches of neural development to findings of this thesis.*

Developmental account	**Can it account for results**	**Relation to findings**
Maturational account	No	Similar brain areas are active in all infants, although their behaviour significantly differs.
Skill learning hypothesis	Partially	The difference in responses between infants and adults may reflect automation due to learning represented as a shift to different neural networks. However, it is unclear whether learning has the same effect in infants as in adults.
Interactive specialisation	Yes	During infancy brain areas do not simply become active, but they become more specialised. Brain areas involved in attention shifts change with age.

In summary, the current results suggest the development of attentional brain mechanisms does not involve simple addition of brain modules. Instead, the areas that are generally involved in attention become more specialised with age during infancy. In

addition, attentional control becomes more automated until adulthood, possibly due to learning, so that frontal areas only need to be involved in more complex shifts in adults. This supports the interactive specialisation idea that neural mechanisms of attention become specialised with age and are affected by learning.

7.3.5 Interhemispheric connections

Interhemispheric connectivity through the splenium of the corpus callosum plays an important role in orienting of attention (Niogi et al., 2010). The current thesis found that in young infants, frontal activation is more pronounced in the contralateral hemisphere, possibly reflecting activation from crossing visual pathways. With increasing age, the ipsilateral hemisphere became more active during attention shifts, coinciding with better behavioural performance in attention shift tasks.

Inter-cortical connections are developing during infancy (e.g. Burkhalter, 1993; de Haan & Johnson, 2003b; Huttenlocher, 1979, 1990; Huttenlocher et al., 1982; Petanjek et al., 2011). This development may be causing the lateralisation of the frontal response to change, allowing it to shift towards the ipsilateral hemisphere. The developmental change might be explained by lateral feedback connections through the corpus callosum. As patient groups with attention impairments show attention shifting difficulties (e.g. individuals with autism: Elison et al., 2013; neglect patients: He et al., 2007), the current study is in line with the idea that interhemispheric connections play a crucial role for shifts of attention.

7.3.6 Implications for neurodevelopmental models of attention

Previous research (reviewed in Chapter 1) suggests:

(1) A SC pathway to initiate saccades
(2) An inhibitory pathway inhibiting saccades to initiate fixations
(3) A visual pathway that can activate SC
(4) A FEF pathway for more refined control of saccades.

This section will apply findings of this thesis to the different pathways and suggest additions to the models.

When covert and overt shifts of attention were compared in adults (Chapter 4), occipital activation in both covert and overt attention tasks suggested that a visual pathway activated the SC (3 above). Furthermore, frontal areas showed positivities when saccade inhibition was required in covert attention tasks, suggesting that the FEF pathway (4 above) may be involved in refined control of saccades by inhibiting saccades to specific directions.

The visual pathway (3 above) is also implicated in attention shifts in the FSP (Chapter 5), as posterior response latencies significantly differed between conditions (competition and non-competition). This difference across conditions can be explained by a visual pathway activating SC at different response latencies to initiate saccades. Further evidence for the role of the visual pathway comes from the study investigating the effect of the visual offset of the central stimulus during attention shifts (Chapter 5). The visual offset accounted for the majority of differences between competition and non-competition conditions, suggesting that it can prompt fixation shifts through the visual pathway (3 above). As visual areas have top-down connections to SC (Schiller & Tehovnik, 2005) the visual offset response may lead to higher activation of SC, facilitating reorientation to new areas.

In infants (Chapter 6) responses were observed in frontal areas (positivity) and in occipital areas (negativity), differing from the responses that were observed in all three adult studies. This suggests that frontal areas, possibly the FEF (4 above), play a more central role for attention shifts in infants than in adults. However, adults show frontal positivities in double target conditions and during covert attention shifts, involving saccade inhibition. Conditions showing frontal positivities have in common that they involve rather complex control in regards to the experience of the subject. Infants have less experience with fixation shifts and therefore require frontal areas to control them. The shifting process is more automatized in adults due to years of learning, therefore requiring less frontal activation. However, tasks that are less commonly practiced in everyday life, like those requiring inhibition of natural saccades, show more frontal activation, suggesting that the frontal pathway (4 above) becomes involved again. This is in line with the suggestion that a frontal pathway is involved in more refined control of attention shifts.

It is possible that frontal areas inhibit shifts to incorrect directions, allowing a more efficient reaction to the correct direction. Frontal positivities build up slowly

within the first 230 ms after target onset in infants and occur fairly late, after around 180 ms in adults, suggesting that this pathway generally works slower than the occipital pathway, possibly resulting in slower saccades when additional control is required.

In summary, results from this thesis suggest that a faster occipital pathway is involved in attention shifts in adults, while a slower frontal pathway may be required for more advanced attentional control and in infants. In conclusion, some additions to previous neurodevelopmental models may be required stating that the visual pathway becomes more involved in attention shifts with age, while the involvement of the FEF pathway decreases (*Figure 7.3*).

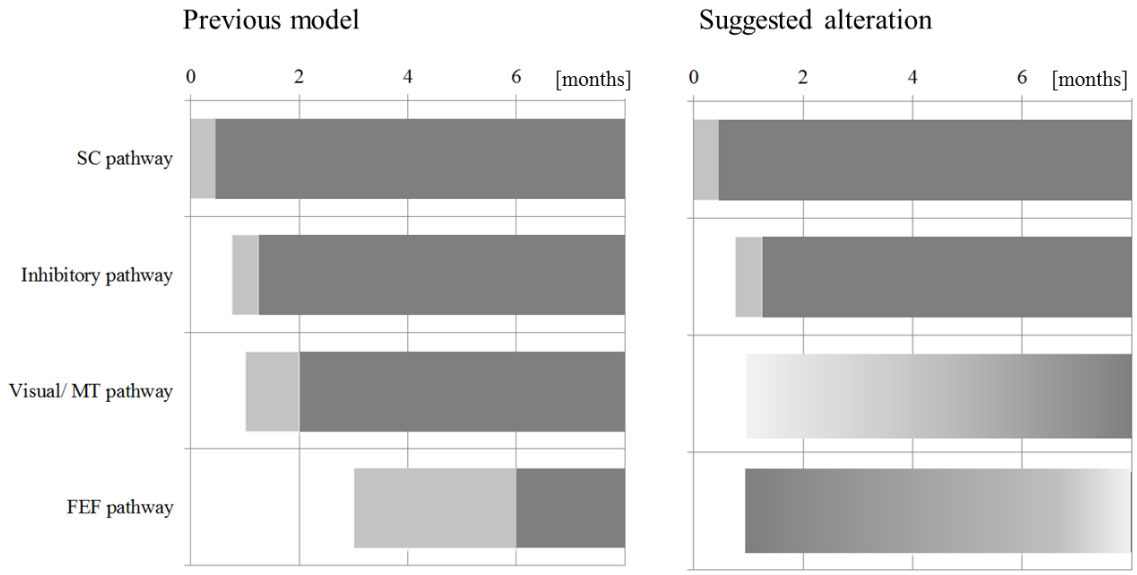


Figure 7.3. Neurodevelopmental model. In addition to previous neurodevelopmental models (left), the current results suggest that the visual/MT and the FEF pathway are already present in the youngest age group (1.5 to 2.5 months) and that their involvement in attention shifts increases for the visual pathway and decreases for the FEF pathway.

7.3.7 Implications for adult attention models

Adult attention network models (Corbetta & Shulman, 2002, 2011) have stressed parietal and frontal (FEF) regions to be involved in top-down control of location of attention. Superior colliculus and frontal eye-fields were suggested to be involved in shifts of attention (Posner & Rothbart, 2007). The literature review in Chapter 1 shows that adult models are mainly based on studies on covert attention that verbally instructed subjects to inhibit eye movements. These studies always involve

inhibition of saccades, which may be the main factor causing the activation. Chapter 4 compared overt and covert shifts, suggesting that positive frontal activation may mainly be due to saccadic inhibition. Therefore, frontal areas might not be related simply to attention but specifically to more complex inhibition mechanisms.

The current experiments found less frontal involvement in adults when they naturally shift attention together with an eye movement (see *Figure 7.4* for a visualisation). It therefore suggests that adult models should be updated with a cautionary note stating that frontal areas may be mainly involved in saccade control rather than in disengagement or attention processes. Adult attention models should consider results of natural attention shift studies without saccade suppression in humans before concluding about the brain areas involved in attention shifts.

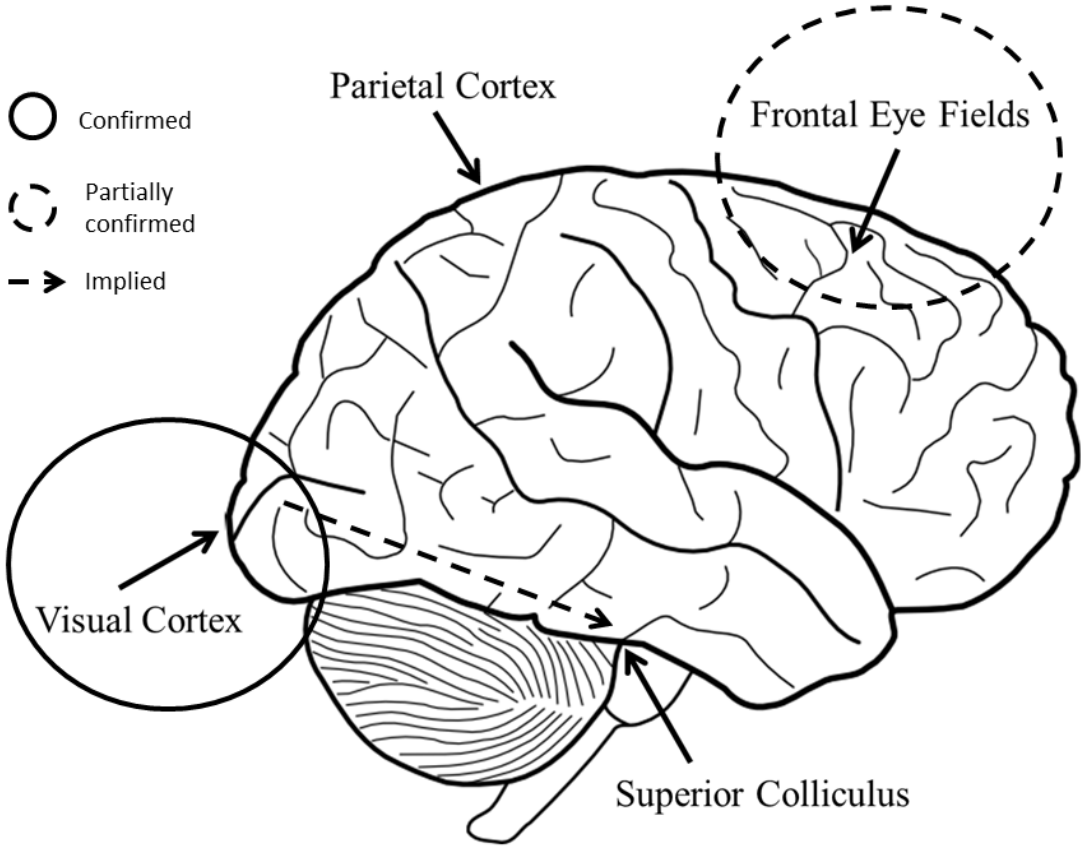


Figure 7.4. Relation of the current findings to previously identified brain areas for attention shifts in adults in Chapter 1, section 1.4.2. The current thesis confirms an involvement of the visual cortex (circled) in attention shifts, possibly through SC. Frontal eye fields (dashed circle) were mainly involved in difficult shifts involving saccade inhibition and parietal involvement was not directly confirmed.

7.3.8 Summary: Neural development of attention

The second overall aim of this thesis was to investigate the neural mechanisms of attention development in infants and adults in regards to current theoretical models of development. The discussion above demonstrates that different neural mechanisms predominate in infants compared to adults and that the development seems to be an interaction of improving connectivity and learning. This has evidence-based implications for current theoretical models of attention. In conclusion, the empirical investigation of brain responses during attention shifts can be used to confirm parts of current neurodevelopmental models and to possibly update other details.

7.4 Contributions of this thesis to the current literature

The current thesis developed a method that can be used to investigate behavioural and neural responses nonverbally and in an automated fashion. Although this method was used in the context of attention development here, it can easily be transferred to other visual research areas. The development of the method, as described in Chapter 2 and Appendices C and D is challenging due to eye movement artefacts and the challenge of temporal alignment of eye tracking and EEG. This thesis critically discussed the problems that can arise with the new method and makes constructive suggestions on how to overcome them (e.g. choice of filter settings, Appendix C, or avoiding noisy data, section 7.2.2). Therefore, this thesis contributes a new method for testing neural mechanisms in nonverbal populations.

Covert attention shifts have been widely studied in the literature; however, nonverbal studies of overt attention shifts are quite rare. The experiments in this thesis provide a direct comparison of covert and overt shifts using the same paradigm and thereby contribute a new investigation of response differences between both types of shifts. There is also a fine-grained investigation of the time course of neural responses during overt shifts, uncovering differences in early ERP latencies between shifts in competition and non-competition conditions. The observed pattern of response provides further support to neural models of attention and prompts suggestions for refinement of these models.

Development of attention shifts in infants has been studied extensively in behavioural research and some researchers have started investigating neural

mechanisms of covert (Richards, 2000, 2001b, 2004, 2005) and overt (Csibra et al., 1998; Csibra et al., 2000) attention shifts in infants. Other studies of overt shifts (Csibra et al., 1998; Csibra et al., 2000) only tested older infants (6 to12 months) whose ability to shift attention is already fairly well developed. Here, overt attention shift mechanisms have been investigated in infants as young as 1.5 months of age. Younger age groups show more disengagement difficulties, making it possible to investigate brain responses during a failure to disengage. The current data contained a number of sticky fixations, allowing for a crude comparison with correct re-fixations and showing differences in the amplitude of brain responses.

The assessment of four age groups from 1.5 to 7.5 months showed that the brain areas involved in attention shifts are similar across infancy, but that the lateralisation changes throughout development, providing support to an interactive specialisation approach of development. The automated FSP can be used as a diagnostic measure of attention development, providing the basis for a clinical measure. However, with present technology EEG may not be a practical developmental measure on a single subject basis, but rather allows investigating overall changes in neural patterns on a group basis with changing age in infants.

In summary, the current thesis provides the development and critical discussion of a new method, allows for a comparison of this covert attention measure with previous overt attention literature, provides new insights into the temporal dynamics of brain responses during overt attention shifts and can therefore add new information to neurodevelopmental models of attention.

7.5 Future research directions

The current thesis developed and used a method that can be applied to several different areas of research. Firstly, due to the diagnostic value of the FSP used throughout this thesis, the method of this thesis may find diagnostic applications for detection of atypical development from an early age on, as reviewed in section 7.2.7. Appendix N describes a pilot study comparing attention shifts measured with eye tracking in typically developing infants with mildly premature infants. The study shows developmental delays in mildly premature infants, confirming the diagnostic value of the method. Future research can test additional preterm born infants and infants who are extremely premature to investigate the effects of the severity of birth difficulties in the

paradigm. This kind of research could furthermore develop guidelines for typical development that could be used to detect developmental disorders from an early age on.

Secondly, developmental delays may be caused by neural dysfunctions. Although EEG may not provide diagnostic measures on an individual basis in infants, it can be used to monitor development on group data for a particular age group. It would therefore be interesting to study atypically developing infants in the same paradigm to explore neural differences in their development.

Thirdly, It would be interesting to follow up the same infants with age in a longitudinal study, to monitor whether developmental delays in premature infants are later resolved during development. A follow up study may be more time consuming but could provide further insights to the time course of developmental delays. Following up later changes throughout childhood may provide further insights to the development. As the current study suggests that infants use more frontal areas to shift attention, while in adults attention is automatized, it would be interesting to explore when the change from frontal to posterior attention pathways occurs during development. Testing older children can provide further insights. Appendix M describes a pilot study using a similar paradigm in children between 6 and 10 years of age. As children can most readily be tested in kindergartens and schools, a portable method is desirable for this age group. In Appendix M a touch screen test was developed that can be used on portable tablets allowing more flexible testing locations. However, recent eye trackers are also easily portable (e.g. Tobii EyeX: Tobii Technology, 2012), enabling flexible testing of older infants and children with the exact same paradigm that was used on adults and infants in this thesis.

As discussed in section 7.2.4, EEG provides a high temporal resolution but currently lacks good spatial resolution. As infant results suggest that several overlapping dipoles may cause the observed effects, a combination of the method with other imaging methods (e.g. MRI) can provide further insights in the sources of the observed responses. Appendix M describes a pilot study in which older children were successfully tested with MRI to investigate measures of neural connectivity (DTI). The preliminary findings suggest that DTI may be a useful tool to investigate neural connectivity related to attention. In particular DTI measures may provide further insights to the role of interhemispheric connections on attention development as discussed in section 7.2.4.

7.6 Final conclusions

This thesis aimed at combining eye tracking and EEG and using this method to monitor overt attention shifts in adults and infants. The first part of the thesis provided critical discussions and experimental investigations of the usability of the method for testing infants and adults. It showed that eye tracking is a suitable method to study attention shifts in non-verbal populations (Chapter 3), and that it can be combined with EEG to investigate neural mechanisms of attention development (Chapter 4). However, the thesis also established that the combination of eye tracking and EEG is prone to distortions by artefacts and data loss that need to be overcome to establish a measure of brain mechanisms to test subjects on a group basis in different research areas (Chapter 2 and 7).

The second part of the thesis provided novel results on the brain mechanisms of attention shifts in adults (Chapter 5) and their development during infancy (Chapter 6). The findings show that occipital areas significantly differ between competition and non-competition conditions in adults, while frontal areas are most involved in attention shifts in infants and show less activation when infants fail to shift. These findings show a non-linear development of attention, possibly due to automation and can be incorporated into current neurodevelopmental models of overt attention. In conclusion, the combination of eye tracking and EEG was successfully used to monitor neural mechanisms of visual attention in typically developing infants and adults.

APPENDICES

Appendix A. How accurate is eye-tracking? An investigation of the spatial accuracy of the Tobii X120

Introduction

Eye-tracking can be used as an automated approach for monitoring fixations and eye-movements (Gredebäck et al., 2009; Wass et al., 2012). Especially in non-verbal populations like infants, eye-movements and fixation durations are a commonly used measure for visual abilities (e.g. Jones et al., 2014) and cognitive processes (e.g Falck-Ytter et al., 2013; von Hofsten et al., 2009; Watanabe et al., 2012). However, the kind of tests that the eye-tracker can be used for depends on whether it is accurate enough to detect fixations within an area on the screen. Spatial accuracy varies depending on the eye-tracker model. This study investigates the accuracy of the Tobii X120 eye tracker. According to the manufacturer the typical spatial accuracy of this model is 0.2-0.3 degrees (Tobii Technology, 2010a). As other eye-trackers' accuracy can differ from the manufacturers' product descriptions when tested by independent researchers (e.g. Johansen, San Agustin, Skovsgaard, Hansen, & Tall, 2011; Morgante et al., 2012; Skovsgaard, Agustin, Johansen, Hansen, & Tall, 2011) this study tested it independently under the optimal conditions suggested by the manufacturer. The aim of this study was to monitor the variance in fixation position measured by the eye-tracker from the actual fixation position of a subject.

Different grades of accuracy are necessary depending on how big the stimuli of interest are and how far they are apart. When using eye-tracking for preverbal infants the stimuli of interest are usually considerably larger than the accuracy range of the eye tracker, as infants' visual acuity is still developing in the first year of life, meaning that they are less sensitive to high-frequency patterns and less able to detect small stimuli. Infants in the first months of life can have lower visual acuity than 0.5 cycles per degree of visual angle (Atkinson, 2000b; Courage & Adams, 1990; Jones et al., 2014; Mayer et al., 1995; Salomao & Ventura, 1995; Teller et al., 1986). To ensure that stimuli are visible to all participants, they should be bigger than the limits of the infants' visual acuity. In order to reliably measure fixation on a stimulus item, it is necessary for the eye-tracker's spatial accuracy to be higher than the size of the stimuli to be used as well as higher than the distance between stimuli. One aim of this study was therefore to

investigate whether the accuracy is sufficient for the infant-friendly stimulus sizes used in studies reported here.

Previous studies on spatial accuracy of other eye-tracking devices did not find a difference in technical accuracy of the eye-tracker between infants and adults (Morgante et al., 2012), and testing accuracy for infants requires assumptions about the infants' fixation behaviour which is difficult to test independently, therefore this study only tested adult subjects. To investigate whether accuracy varies across screen positions, adults were instructed to fixate on a dot moving between different locations and deviations of measured fixation coordinates from actual coordinates were investigated.

Method

Design

In a within-subject design the absolute deviation of the fixation position (X and Y coordinates) measured by the Tobii X120 eye-tracker from the actual position of a target was compared between different target positions on a screen (Figure A.1).

Participants

Thirty-eight students (mean age = 25.84 years, *SD* = 4.71 years, 4 male) from University College London (UCL) volunteered to participate in return for sweets. The number of participants was determined by a power analysis in G*Power 3 (Faul, Erdfelder, Lang, & Buchner, 2007). The study was approved by the UCL ethics committee (Ref. number: CPB/2013/011).

Material and Stimuli

Stimuli were generated using MATLAB (version 7.11.0 (R2010b)) as presentation program on a Dell computer with Linux Mint 14 as operating system and presented on a 21.5 inch LCD monitor. A Tobii X120 remote eye-tracker tracked the participants' eye-movements. Gaze positions were sampled at a rate of 60Hz. Stimuli were green dots moving on a black screen. They had a diameter of 0.7 degree of visual angle when viewed from a fixed distance of 65 cm from the screen (70 cm from the eye-tracker as recommended by Tobii Inc.; Tobii Technology AB, 2008).

Procedure

Participants were seated in front of the computer screen with their head comfortably positioned on a chin rest that ensured that the optimal position from the eye tracker as suggested by the manufacturer was maintained. Initially, the eye-tracker was

calibrated on each subject individually using a five-point calibration routine, which took approximately 2-3 minutes. Afterwards, the experiment began, in which a small green dot appeared on the middle of the screen and was moved to 13 locations (Table A.1) by disappearing from one position and appearing on another at the same time (Figure A.1). The dot appeared in every position displayed in Figure A.1, coordinates of which can be derived from Table A.1. Participants were instructed to follow this dot with their gaze and fixate on its centre. Completing the study took approximately 5 minutes.

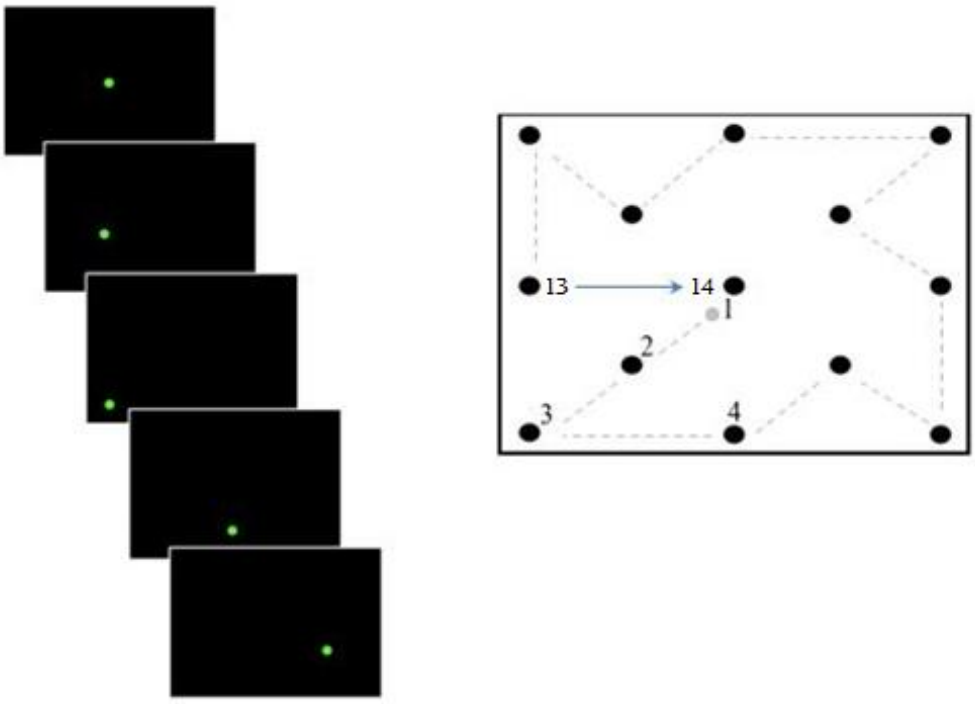


Figure A. 1. Schematic overview of the order of stimulus onsets.

Table A. 1. *Target positions used in the x and y dimension from left to right and bottom to top respectively, displayed in degree of visual angle (and pixel).*

Target position x [degree (pixel)]	Target position y [degree (pixel)]
-16.7 (-765)	-9.9 (-450)
-8.6 (-390)	-5.1 (-233)
0	0
8.6 (390)	5.1 (233)
16.7 (765)	9.9 (450)

Eye-tracking analysis

Eye-tracking data was collected during the appearance of dots. The raw eye-tracking data was extracted separately for x-coordinates and y-coordinates of the fixation positions. The first 1.5 seconds after dot onset were excluded from the analysis to ensure that no data from the saccadic shift towards the target was included in the analysis. The data until the disappearance of the dot (0.5 sec = 30 samples) was extracted and averaged across samples for each individual subject, separately for each position and separately for x- and y-coordinates.

Results

Differences between gaze positions measured by the eye-tracker and actual gaze positions were calculated separately for x- and y-dimensions. The mean absolute differences were 0.82 degree (*SD* = 1.06) in the x-dimension and 0.83 degree (*SD* = 1.06) in the y-dimension. Table A.2 and Table A.3 show the differences separately for different target positions. One-sample t-tests confirmed that the measured absolute values significantly differed from the actual values in x-dimension, $t(581) = 18.74$, $p < .001$ (Table A.2), and in the y-dimension, $t(581) = 18.82$, $p < .001$ (Table A.3). There was no significant difference between the deviations in x- and y-dimensions, $t(581) = -0.14$, $p = .892$. Measured and actual fixation positions differed more in locations in the upper visual field than in the lower visual field (Figure A.2).

Table A. 2. *Differences of measured fixations from centre of fixation dot in the **x-dimension** in degree depending on the position of the target. Numbers displayed are the mean (and SD) of absolute deviations in the x-dimension.*

		Target position x [degree (pixel)]				
		-16.7 (-765)	**-8.6 (-390)**	**0**	**8.6 (390)**	**16.7 (765)**
Target position y [degree (pixel)]	**9.9 (450)**	0.74 (1.31)		0.38 (0.42)		1.00 (1.78)
	5.1 (233)		0.78 (0.74)		0.73 (0.70)	
	0	1.19 (1.37)		0.34 (0.42)		1.15 (1.32)
	-5.1 (-233)		0.85 (0.73)		0.87 (0.80)	
	-9.9 (-450)	1.37 (1.26)		0.33 (0.37)		1.40 (1.22)

Table A. 3. *Differences of measured fixations from centre of fixation dot for the* ***y-dimension*** *in degree depending on the position of the target. Numbers displayed are the mean (and SD) of absolute deviations in the y-dimension.*

		Target position x [degree (pixel)]				
		-16.7 (-765)	**-8.6 (-390)**	**0**	**8.6 (390)**	**16.7 (765)**
Target position y [degree (pixel)]	**9.9 (450)**	0.79 (1.37)		1.15 (1.44)		1.18 (2.06)
	5.1 (233)		1.06 (1.06)		1.26 (1.02)	
	0	0.77 (0.81)		0.84 (0.73)		0.88 (0.81)
	-5.1 (-233)		0.48 (0.51)		0.62 (0.63)	
	-9.9 (-450)	0.73 (0.72)		0.46 (0.76)		0.64 (1.17)

To test for biases in a specific direction the raw values of fixation positions were compared to target positions. One-sample t-tests showed a significant bias to the left side in the x-dimension, $t(581) = -6.63$, $p < .001$, and a significant bias towards the top in the y-dimension, $t(581) = 2.73$, $p = .007$.

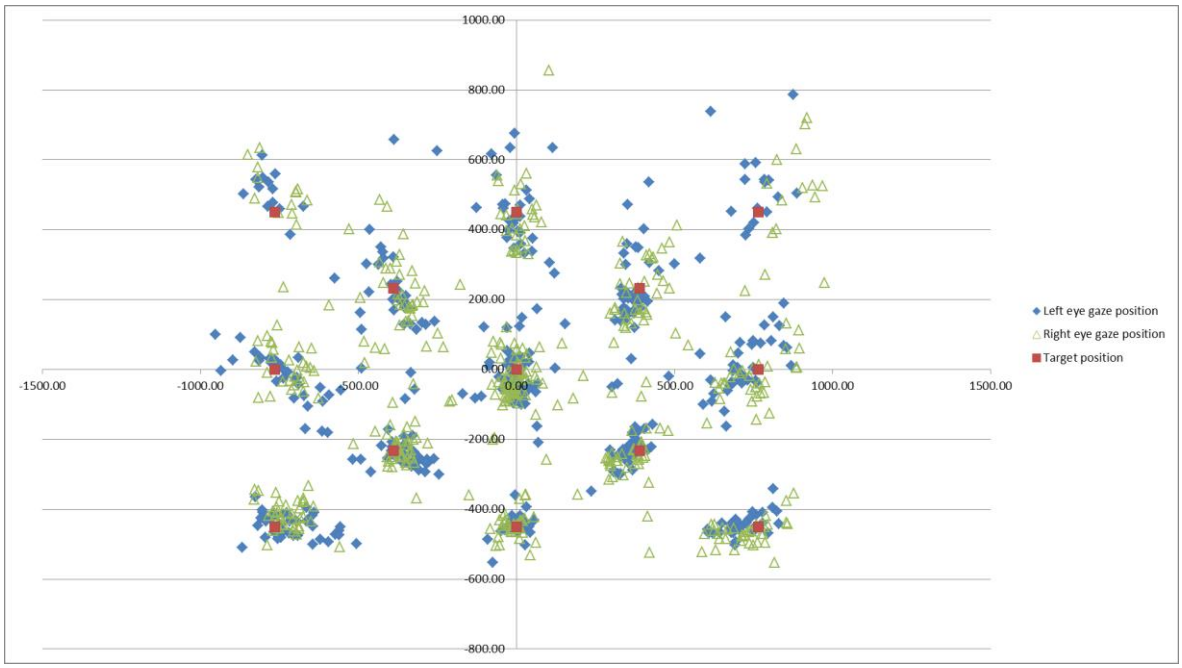


Figure A. 2. Measured fixation positions scatter around the actual target positions (red square). Coordinates of measured gaze are displayed separately for the left and the right eye. Axes are labelled with size in pixel.

Discussion

This study aimed to investigate the spatial accuracy of the Tobii X120 eye-tracker. Results show that the mean absolute difference between measured and actual gaze position was approximately 0.8 degree with a standard deviation of 1 degree. This value is higher than the 0.2-0.3 degrees suggested by the manufacturer (Tobii Technology, 2010a), meaning that fixation position measures deviate from the actual fixation positions. However, the magnitude of the distortion is smaller than stimuli sizes and distances used for infant studies, as objects of this size are usually too small to be reliably detected with the visual acuity that some of the younger infants have (Atkinson, 2000b; Courage & Adams, 1990; Jones et al., 2014; Mayer et al., 1995; Salomao & Ventura, 1995; Teller et al., 1986). Although the distortion seems to be slightly greater in the top area of the screen, significance levels do not confirm this observation, indicating that stimulus location should only have a minor effect on the accuracy of the eye-tracker.

For research with stimuli and distances between stimuli that are as small as the distortion results should be treated carefully. However, for the studies in this thesis, in which stimuli and distances will be greater than the inaccuracy, the spatial inaccuracy is expected to have a negligible effect on the results. Furthermore, the major concern in data analysis in this thesis is with the timing of saccades and determining whether they are in the correct direction towards the target. ***In conclusion, eye-tracking results should be treated with care but the spatial accuracy should be sufficient for the purpose of this thesis.***

Appendix B. The effect of stimulus size and eccentricity on saccadic latencies

The Fixation Shift Paradigm (FSP) is a well-established measure of attention shifts. Differences in saccade latencies between competition and non-competition conditions have been demonstrated reliably in different set ups and using different target stimuli (e.g. Aslin & Salapatek, 1975; Atkinson et al., 1992; Hood & Atkinson, 1993; Matsuzawa & Shimojo, 1997). The most commonly used stimuli are a central schematic face and peripheral high contrast bars that are big in size, being well above the acuity threshold and therefore particularly suitable for young infants (Atkinson et al., 1992; Hood & Atkinson, 1993). However, the stimuli used in the similar gap-overlap paradigm sometimes differ in size and eccentricity from the FSP stimuli. For example, Csibra et al. (1997) used a gap paradigm task to monitor ERPs during fixation shifts and they used stimuli with a size of 0.33° that were displayed at a eccentricity of 5°. However, this thesis used stimuli modelled on the FSP, which were therefore higher contrast, bigger (3.1°x13.2°) and presented at a greater eccentricity (12.9°).

The current study aimed at investigating potential differences in saccadic latencies in response to stimuli of different sizes and eccentricities to test whether these stimulus features may affect findings and comparison between studies.

Method

Participants

Twenty-two healthy adults (M_{age} = 20.09 years, *SD* = 1.39, 8 male) with normal or correct to normal vision volunteered to participate in the study after informed consent. The study was approved by the UCL ethics committee (Ref no. CPB/2014/007).

Design and Stimuli

In a 2×2 factorial design the effect of target size (Csibra's size: 0.33° square (Csibra et al., 1997) or Kulke's FSP size: 3.1°x13.2° rectangle (Kulke & Wattam-Bell, 2013; Kulke, Wattam-Bell, Atkinson, & Braddick, 2014a; Kulke et al., 2014b)) and eccentricity of the target (5° or 12.9° from the centre) on saccade latencies towards a target were measured. Matlab7.11.0 (R2010b) was used to generate the stimuli on a CRT monitor (Samsung). A Tobii X120 eye tracker monitored eye movements of participants.

Conditions were completed in four separate blocks. In all conditions a central fixation point was visible throughout the trials. After a random inter-trial interval between 0.5 and 2.5 sec a target pseudo-randomly appeared in the left or right periphery until the subject looked at it. Eccentricity and size of the target were varied between blocks leading to four different conditions: (1) big stimulus (3.1°x13.2° rectangle) at high eccentricity (12.9°), (2) small stimulus (0.33° square) at high eccentricity, (3) big stimulus at small eccentricity (5°) and (4) small stimulus at small eccentricity (see Figure B.1 for a visualization of the trials). Orders of blocks were randomized for each participant.

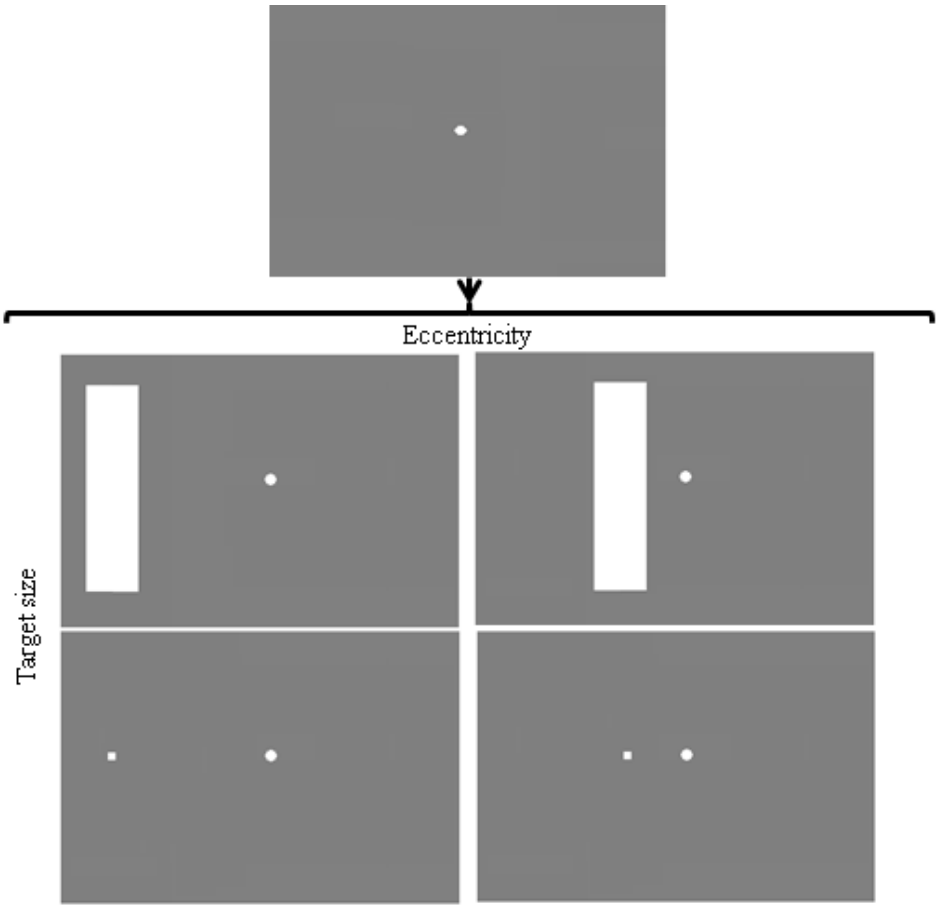


Figure B. 1. Conditions differ in target size and eccentricity.

Procedure

Participants were seated at a distance of 65 cm from the computer screen. They completed a standard 5-point calibration routine, which took no longer than 3 minutes. After the calibration, 4 blocks were presented in random order with short breaks between blocks. Each block contained 100 trials, and lasted approximately 5 minutes. The entire experiment took approximately 30 minutes to complete. Participants were

instructed to fixate at the central point, and look at the target as quickly as possible after they appeared.

Results

An ANOVA was used to analyse the effect of target size, eccentricity and their interaction effect on saccade latency. Means and standard deviations of saccade latency between participants for different conditions are displayed in Table B.1. Saccade latencies are displayed in ms throughout this section.

Table B. 1. *Means and standard deviations of saccade latencies (in ms) towards stimuli of different sizes and eccentricities*

		12.9° eccentricity	**5° eccentricity**
0.33° target	Mean	275	272
	SD	41.8	58.0
3.1°x13.2° target	Mean	261	290
	SD	46.0	65.1

There were no significant main effects of target size, $F(1, 172) < 1$, $p = .804$, or eccentricity, $F(1, 172) = 2.85$, $p = .093$, but a small, marginally significant interaction effect of target size and eccentricity, $F(1, 72) = 3.86$, $p = .051$.

Further analyses showed that for a target size of 3.1°x13.2°, participants reacted significantly faster for targets at an eccentricity of 12.9° ($M = 261$, $SD = 46.0$) than at 5° ($M = 290$, $SD = 65.1$), $F(1, 86) = 6.02$, $p = .016$, $d = 0.515$. Eccentricity did not have a significant effect on saccade latency when the stimulus was a 0.33° square, $F(1, 86) < 1$, $p = .836$. Latency did not significantly differ between target sizes at an eccentricity of 5°, $F(1, 86) = 1.85$, $p = .178$, $d = 0.292$, or an eccentricity of 12.9°, $F(1, 86) = 2.19$, $p = .143$, $d = 0.319$.

Discussion

There were no significant main effects of target size or eccentricity on saccade latency. This is in line with the hypothesis that target features only have a negligible effect on saccade latencies. However, there was a non-significant interaction of target

size and eccentricity, showing that subjects responded slower to the big target stimulus when it was closer to the centre of the screen. The longer latencies may be due to an implicit tendency to look at the centre of a target stimulus (Henderson, 1993). For a large target of small eccentricity, subjects may have more angular uncertainty about the centre of the target, making it more difficult to compute the direction they should make the saccade in. It is therefore recommended to use smaller stimuli at small eccentricities and bigger stimuli at greater eccentricities, i.e. to scale the stimulus in proportion to the eccentricity.

The current study shows that stimuli that are commonly used for the FSP (big size, great eccentricity) elicit saccades at comparable latencies to the stimuli commonly used in the gap overlap task (small size, small eccentricity). ***In conclusion, the observed effects in both paradigms can be compared independent of the size and eccentricity of stimuli they use.***

Appendix C. Effects of filter settings on ERP amplitude for trials containing task relevant saccades

Overt attention shifts involve eye-movements as a fixed constituent of all trials. Eyes have an innate polarity, being positive at the side of the cornea and negative at the side of the retina (Jervis et al., 1988). Due to this polarity, eye-movements cause a change in electrical potentials measured at the scalp surface. It is therefore generally recommended to excludes any trials from analyses that contain eye-movements as artefacts (see e.g. Jervis et al., 1988; Luck, 2005). This was no challenge for previous research on covert attention shifts instructing subjects to inhibit eye movements during trials (e.g. Anllo-Vento & Hillyard, 1996; Eimer et al., 2005; Eimer et al., 2002; Martinez et al., 1999; Praamstra & Oostenveld, 2003; Shomstein et al., 2012; Yamaguchi et al., 1994, 1995) and only excluding occasional trials due to eye movements. However, when studying overt attention shifts, each trial is bound to contain an eye-movement, making it impossible to exclude these trials.

To avoid confounds with eye-movement artefacts, short intervals (180 ms) were extracted in this thesis, so that most saccades occurred after the extracted time window. Furthermore, eye-tracking data was used to exclude trials with very early saccades, reducing the effect of eye movement artefacts. However, guides to ERP methods recommend digital filters to be applied to the EEG data before these time windows are extracted to avoid "edge" artefacts (e.g. Luck, 2005; Tanner et al., 2015), meaning that the data still includes saccades at the time of filtering. Previous research suggests that high pass filters of 0.3 Hz and above can lead to artificial responses of opposite polarity preceding an actual response (Tanner et al., 2015). This section aimed to explore the effects of different high pass filter settings on the data to investigate whether eye-movements lead to systematic distortions of the data.

Method

Conditions involving saccadic eye movements compared to manual responses of the EEG data set collected for Chapter 4 were pre-processed using the same methods as described in Chapter 2 (section 2.3), only differing in the criterion used for high-pass (HP) filtering. HP filters of 0.2, 0.1, 0.01 and 0 Hz were compared[6].

[6] The NetAmp 300 amplifier automatically applies an analogue low-pass filter at 6 kHz and after the analogue-digital conversion of the data applies a 4 kHz low-pass filter. No further online high-pass or low-pass filters were applied to avoid data distortion.

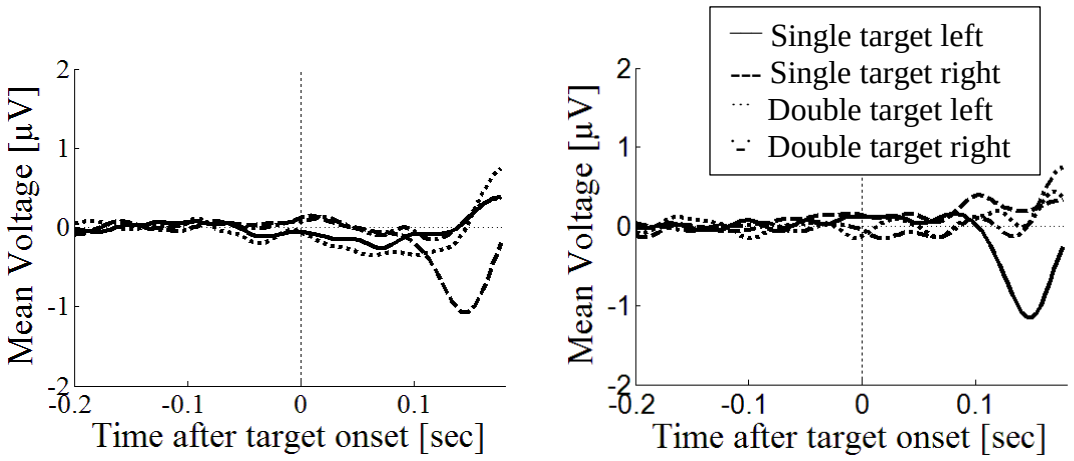
Results

Exploration of different filter settings

Wave plots of the fronto-central responses measured in lateral clusters between electrode locations F and FC in the 10-10 system (Chapter 2, Figure 2.5) in different filter conditions are displayed in Figure C.1 and C.2. For tests with manual responses, different filter settings did not lead to significantly different wave forms (Figure C.1).

MANUAL RESPONSE

a) Manual conditions with HP filter set to 0.2 Hz



b) Manual conditions with HP filter set to 0.01 Hz

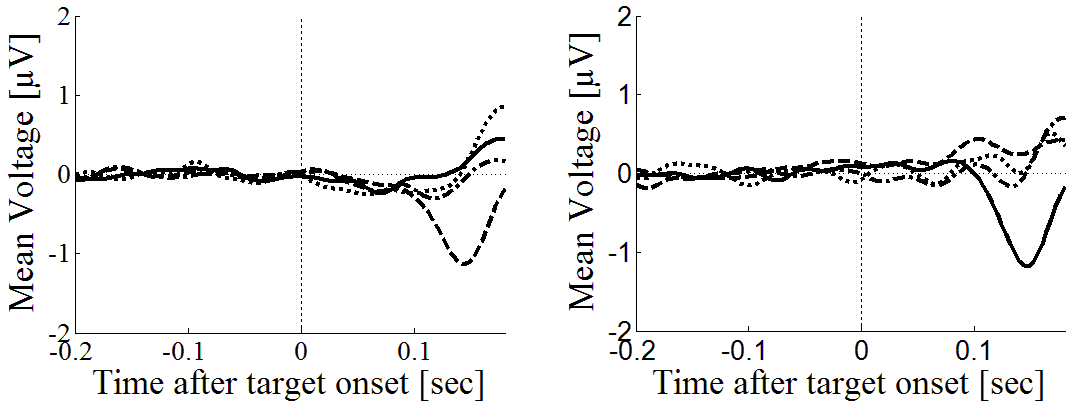


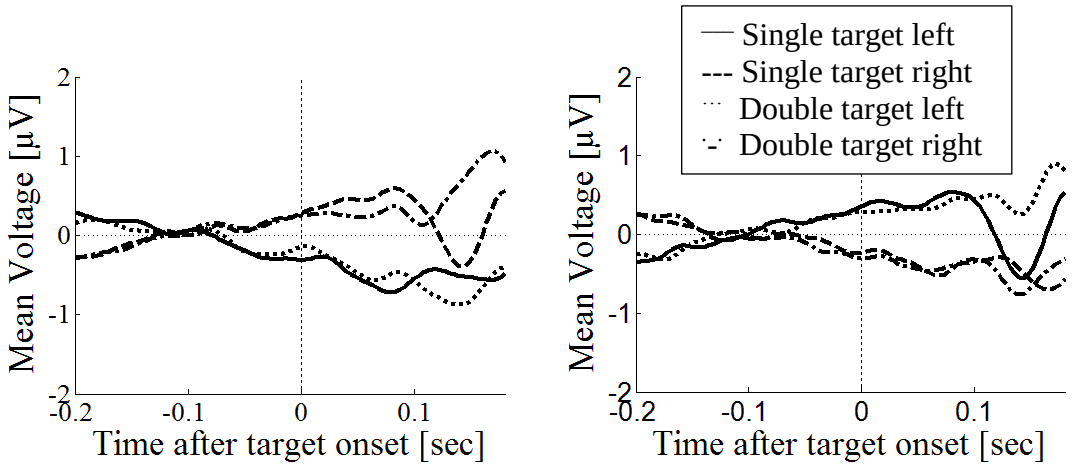
Figure C. 1. Wave plots of the fronto-central response for manual response conditions in the left hemisphere (left) and the right hemisphere (right) of the brain. Responses are similar for both filter settings, suggesting that filters do not cause significant distortion of ERP data before covert attention shifts.

However, for saccadic response conditions the highest filter setting of 0.2 Hz induced an artefactual early response in fronto-central areas that was positive

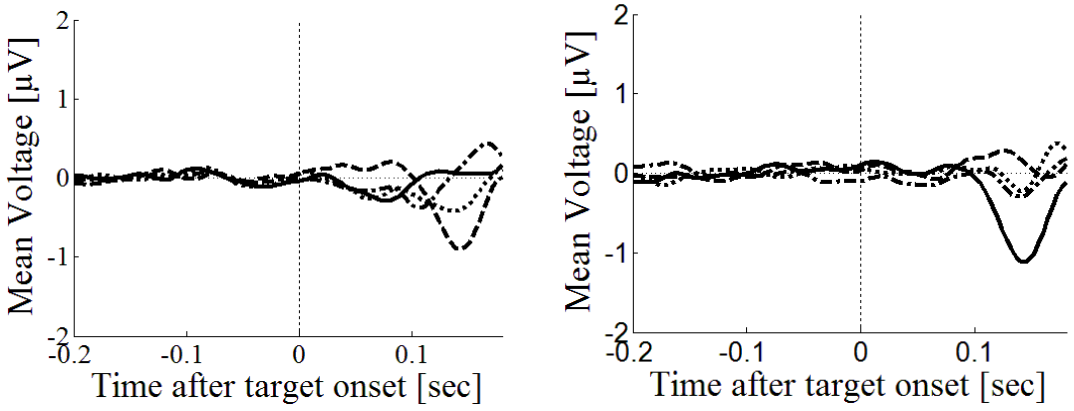
contralateral and negative ipsilateral to the direction of the eye-movements, being a slow wave of opposite polarity of the eye movement artefact (Figure C.2a). Filters can lead to smeared responses occurring before the actual response of opposite polarity (Luck, 2005). As eye-movement artefacts are positive ipsilateral to the direction of movement, this response reflects this kind of artefact of opposite polarity. The response was still marginally visible in the left hemisphere for 0.1 Hz filters (Figure C.2b) but disappeared for lower HP filter settings (C.2c and C.2d).

SACCADE

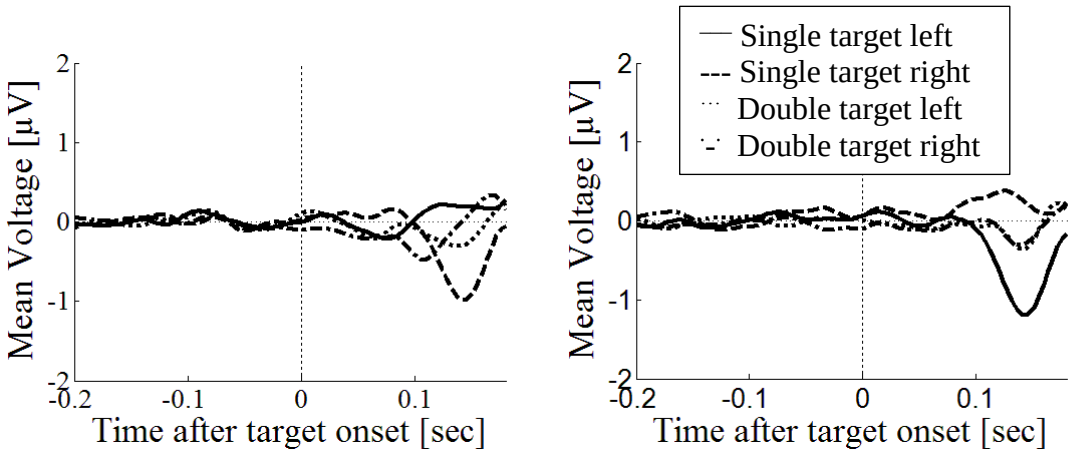
C.2a) Saccade conditions with HP filter set to 0.2 Hz



C.2b) Saccade conditions with HP filter set to 0.1 Hz



C.2c) Saccade conditions with HP filter set to 0.01 Hz



C.2d) Saccade conditions with HP filter set to 0 Hz

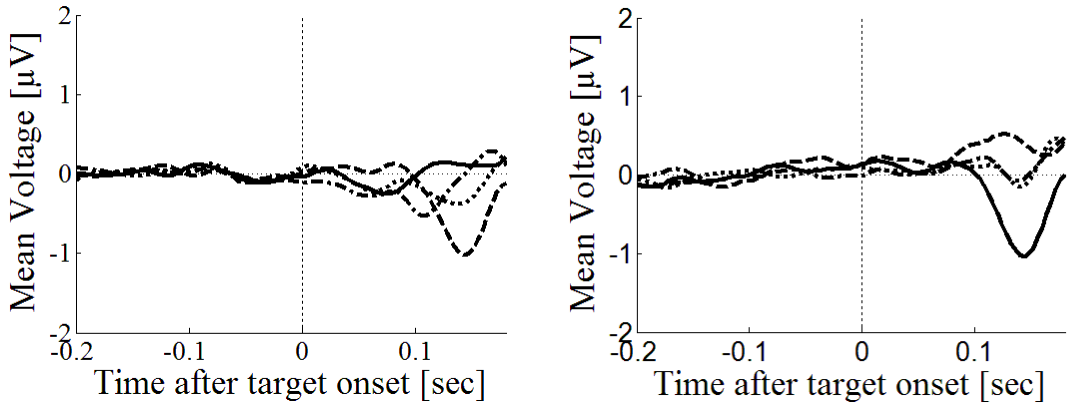


Figure C. 2. ERP waveform of the fronto-central response for saccade conditions in the left hemisphere (left) and the right hemisphere (right). A 0.2 Hz filter (C.2.a) induces an artificial slow wave response that is positive contralateral and negative ipsilateral to the subsequent eye movement direction.

Analysis of the artefactual response

The artefactual response induced when using a 0.2 Hz high pass filter was further analysed by calculating peak amplitudes in different electrode locations for individual subjects separately. Table C.1 displays the labels of the electrodes extracted. Linear mixed models were computed including participants as random effects and electrode location, number of targets, brain hemisphere and response type as fixed effects.

Table C. 1. *List of lateral electrodes that were extracted to analyse the scalp distribution of the fronto-central response. The electrode numbers in the Geodesic Sensor Net are displayed and corresponding electrode labels in the 10-10 system are reported in brackets.*

Location	Left	Right
Frontal	24 (F3)	124 (F4)
Fronto-central	29 (FC3)	111 (FC4)
Central	36 (C3)	104 (C4)
Centro-parietal	42 (CP3)	93 (CP4)
Parietal	52 (P3)	92 (P4)

Peak amplitude showed a significant effect of brain hemisphere, $F(1, 878) = 87.43$, $p < .001$, $d = 0.533$, and a significant interaction effect of electrode location and hemisphere, $F(4, 878) = 4.78$, $p < .001$. Peak amplitudes were greater in the contralateral hemisphere ($M = 0.83$ µV, $SD = 1.85$) than in the ipsilateral hemisphere ($M = -0.07$ µV, $SD = 1.53$). Figure C.3 shows that the hemispherical difference is greater in frontal areas and decreases towards parietal areas, which is in line with eye movements having a greater impact on the voltage measured at frontal electrode sites and decreasing towards posterior sites.

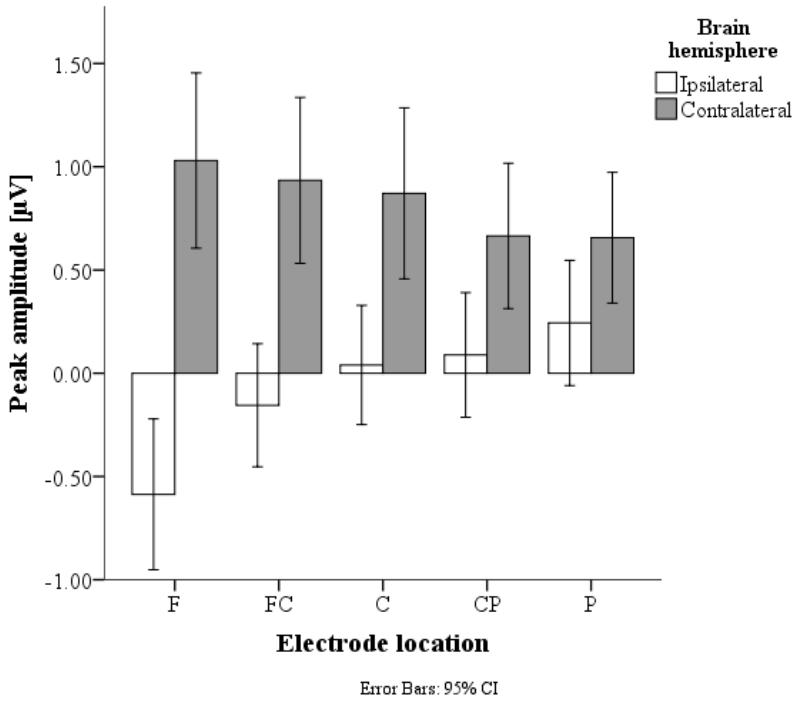


Figure C. 3. Artificial responses are more lateralised in frontal regions (F) and decrease towards parietal regions (P).

Detailed analyses of the time window

To further analyse the temporal changes of the fronto-central artefact four different time windows were extracted in fronto-central regions: 0-50 ms, 50-100 ms, 100-150 ms and 150-200 ms. Mean amplitudes in these time windows were compared using a mixed linear model including participants as random effects. There was no significant effect of time window on mean amplitude, $F(3, 682) = 1.68$, $p = .170$, suggesting that the artefact is a slow wave spread across time. Figure C.4 displays the change in lateralisation over time.

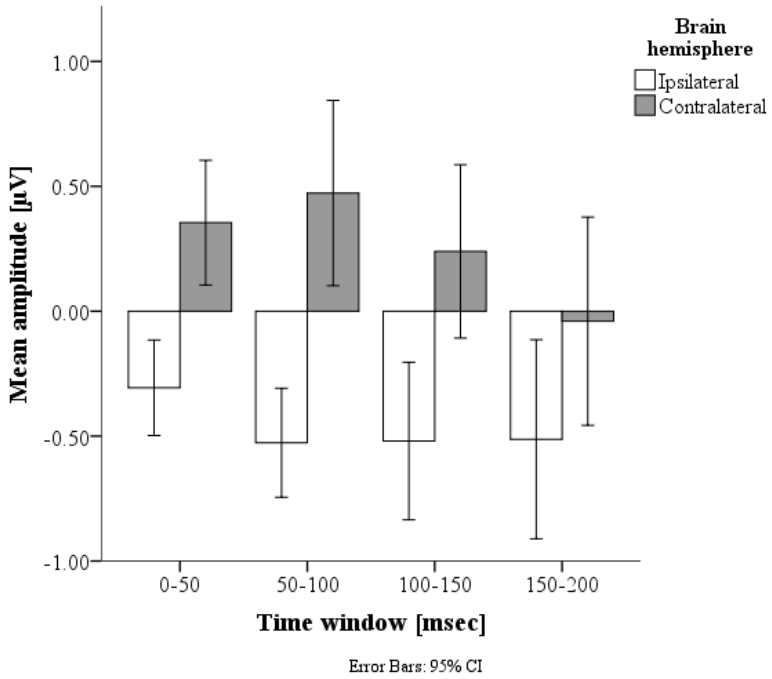


Figure C. 4. Change in lateralisation over time. The figure suggests that the difference between the hemispheres is greatest between 50 and 100 ms, although the interaction is not significant.

Time window before stimulus onset

To further explore the onset of the fronto-central response, the mean amplitude in the time window before stimulus onset from -50 to 0 ms was analysed with a linear mixed model with participants as random effects and number of targets, brain hemisphere, brain side and response type as fixed effect. There was a significant effect of hemisphere on mean amplitude, $F(1, 154) = 5.28$, $p = .023$, Figure C.5, corroborating that this response is not related to the stimulus but rather an artefact created by filtering.

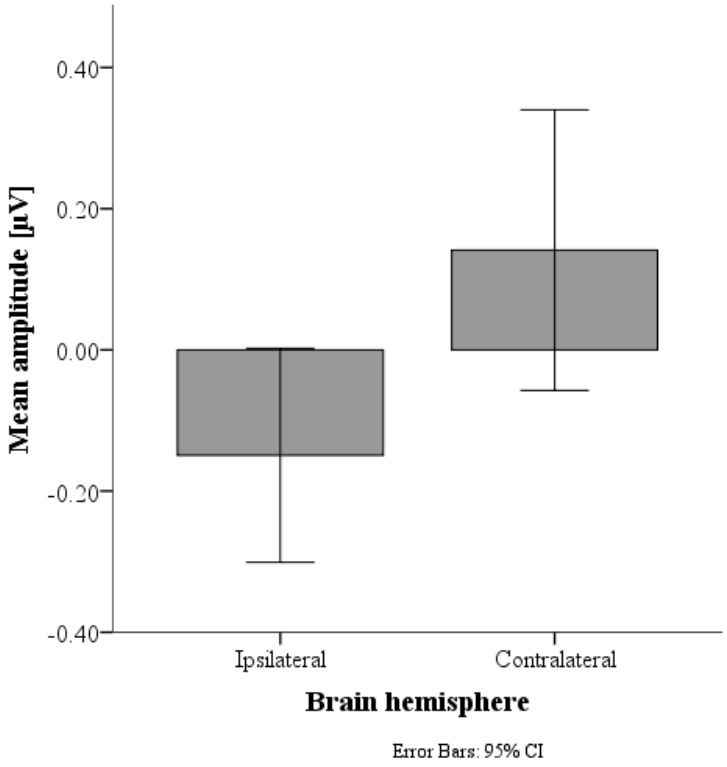


Figure C. 5. The mean amplitude before target onset was significantly higher in the contralateral than in the ipsilateral hemisphere.

Discussion

The analysis shows that different filter settings can induce artefactual responses in data containing regular saccades. Responses even had a statistically significant effect on ERPs. Detailed analyses confirm the artificial nature of the response, showing that the measured slow wave is more lateralised in anterior areas, which are more affected by eye-movements, than in posterior areas. It was furthermore already significantly lateralised before target onset, suggesting that it is unrelated to visual input.

While filter settings had a negligible effect on ERP data for covert attention shift in this demonstration, they should be carefully considered when investigating overt shifts of attention. One of the main purposes of filters is to remove artefacts due to drifts over time. As drifts are usually slow waves, they should only have a small effect on the short interval of 180 ms post-target extracted in this study as long as trials are baseline-corrected to account for slow drifts over time. Given that high-pass filtering can induce artefactual responses due to saccades, the high-pass filter criterion was set to the minimum standard criterion recommended by Luck (2005) of 0.01 Hz for adults tested in this thesis to avoid artefacts. As drift artefacts are more common in infants, a higher

high pass filter criterion of 0.1 Hz is recommended (Hoehl & Wahl, 2012) and as distortions for this cut off were negligible the criterion was used for infant analyses. ***In conclusion, studies of overt attention shifts are prone to filter artefacts induced by high-pass filtering and criteria should therefore be set as low as possible.***

Appendix D. A method to determine the temporal accuracy of EEG data

The interpretation of ERP timing depends on accurate information about the interval between stimulus events and time points in the EEG record. This depends both on the timing of the digital system generating the stimulus and the triggers it sends to the EEG system, and on any delays within the EEG recording system. As Electrical Geodesics Incorporated has a record of undocumented timing delays and technical errors (e.g. Electrical Geodesics, 2014), and as the response timing of monitors may vary, it was necessary to make an empirical measurement of any time delay affecting the alignment of the EEG record and the appearance of the stimulus on the screen. This study aimed at investigating possible delays by stimulating the EGI caps with a visual signal from a photodiode picking up the target onset.

Method

The standard set up for previous studies was used to keep conditions as similar as possible. Stimuli were two white bars presented on the left and the right side of the screen against a grey background (Figure D.1). In contrast to the experimental studies the bars were not reversing in contrast, so that stimulus onset was unambiguous. A light-sensitive diode (Sharp OPIC Light Detector, GA1A1S202WP) was attached to the screen on the position where bars appeared, either at the top of the bars or at the bottom of the bars. The diode was powered by batteries and the signal was led through a coil (Figure D.2) that was placed on the head of a compliant volunteer subject. A Geodesic Sensor Net was placed over the coil and applied as usual with impedances adjusted to less than 90 kΩ (Figure D.3). The EEG signal was then recorded as usual. The subject remained still with her eyes closed during EEG recording to avoid ERPs interfering with the signal recorded from the diode. EEG data was processed with the same Matlab programme used for the previous studies. However, the low-pass filter was adjusted to 120 Hz (Nyquist frequency of the monitor refresh rate), while the high pass filter was 0.2 Hz. The data was segmented into epochs from -0.4 to 0.8 ms around the trigger. The maximum voltage in this time range was determined to calculate when the onset of the stimuli, as recorded from the diode was picked up in the EEG data. Four recording sessions were conducted, in each of which 30 trials were completed. In two sessions the diode, was placed on the bottom of the white bar, in one session it was placed at the top

of the white bar and in one session black cardboard was placed between the diode and the white bar, to confirm that the detected signal stemmed from the stimulus.

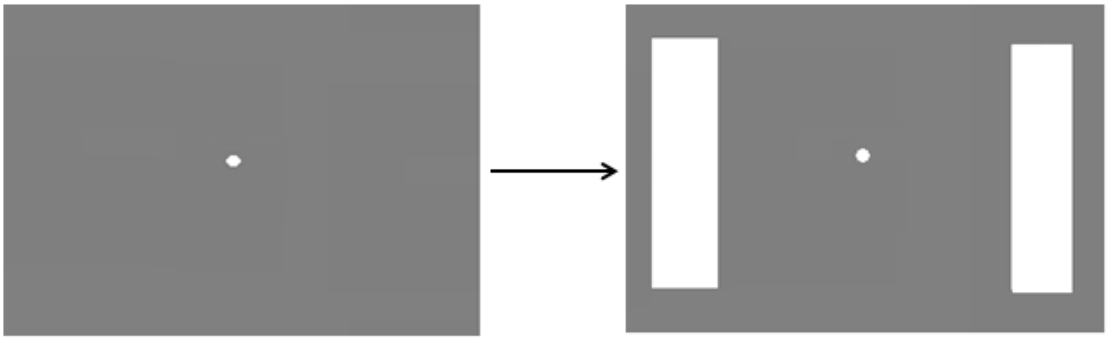


Figure D. 1. Stimuli used for the timing test. As in previous studies the trial started with a fixation dot appearing for a random inter-trial interval between 0.5 and 2.5 sec, after which white bars appeared on both sides of the screen.

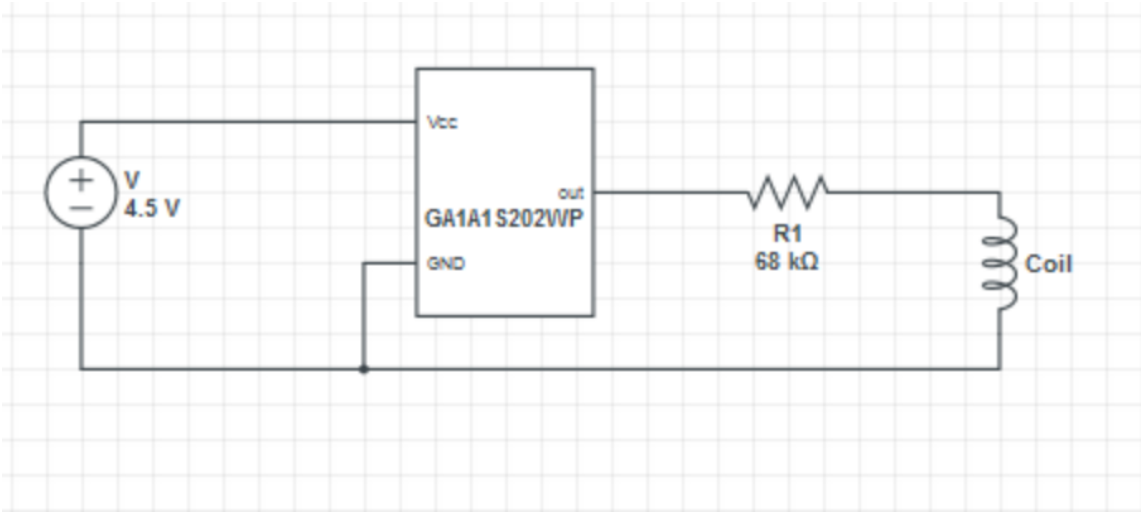


Figure D. 2. Circuit used for the test. A power supply is connected to a diode (GA1A1S202WP), the output of which is lead through a 68 kΩ resistor to the coil which was placed on the subject's head underneath the Geodesic Sensor Net.

Figure D. 3. A wire (blue) connected to the light-sensitive diode is coiled up and placed under the net that is applied under the usual conditions.

Results

A clear peak could be determined in all sessions in which the diode was attached to the screen but not when it was covered by black cardboard (Figure D.4), suggesting that the detected signal was elicited by the stimuli presented on the screen.

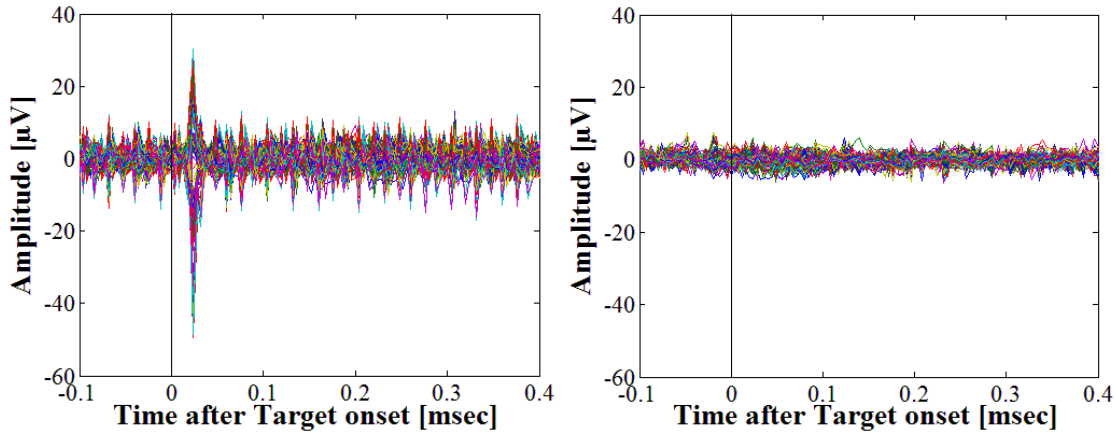


Figure D. 4. Average response across 30 trials measured by all electrodes (colour coded) of the net when the diode was connected to the screen (left) or when the diode was covered with black cardboard (right). The left plot shows an oscillating response at the monitor refresh rate and a peak briefly after target onset (symbolised by the vertical

line), when the luminance change on the screen was detected by the diode, while the right plot contains random noise and no response from the diode.

The peak occurred on average 28 ms after trigger onset, with an average onset of 18 ms after trigger onset (Table D.1), peaking slightly earlier at the top of the stimulus than at the bottom, which is in line with the monitor refreshing from the top to the bottom of the screen.

Table D. 1. *Peak delay detected in the three different runs.*

Diode location	Peak delay in ms	Onset delay in ms
Bottom centre of bar (1)	28	20
Bottom of bar (2)	32	20
Top of bar	24	16

Discussion

The signal elicited by the diode was measured by the EEG system on average 28 ms after it appeared on the screen. This suggests that there is a small delay in the EEG data; however, this delay does not lead to an overlap of ERPs with the baseline period, but rather leads to the EEG signal arriving later in relation to the trigger than it actually occurs. The baseline is therefore not confounded with responses to a subsequent target, implying that peak amplitudes relative to the baseline are unaffected by the delay. The delay is approximately equivalent to one frame at a monitor refresh rate of 60 Hz. Considering that the monitor refreshes from the top left to the bottom right, the shortest time interval (24 ms) should be used to correct for the delay, as this is when the stimulus starts appearing. In particular, using the shortest delay ensures that the baseline period is not confounded with ERPs in response to the stimulus. The temporal inaccuracy should be considered or corrected when interpreting ERP latencies. As the delay is fairly constant between conditions it does not affect the differences between conditions, but only absolute latency values. ***In conclusion, a simple combination of a diode and a coil placed underneath and EEG cap can be used to determine the temporal delay of an EEG set up and this delay should be corrected for during the analysis.***

Appendix E: Comparison of infant and adult fixation positions (Chapter 3)

Two adult subjects were tested under identical conditions as the infants in Chapter 3, to investigate whether differences in measured gaze position between age groups may be due to a spatial inaccuracy of the eye tracker because it was calibrated on an adult before testing.

A comparison of infants with adults showed a significant effect of age group on fixation position, $F(1, 2) = 4.24$, $p = .021$, with smaller distances from the target stimulus in older infants and adults than in younger infants (Figure E.1). The difference between older infants and adults was not significant, $F(1, 2) = 1.23$, $p = .278$.

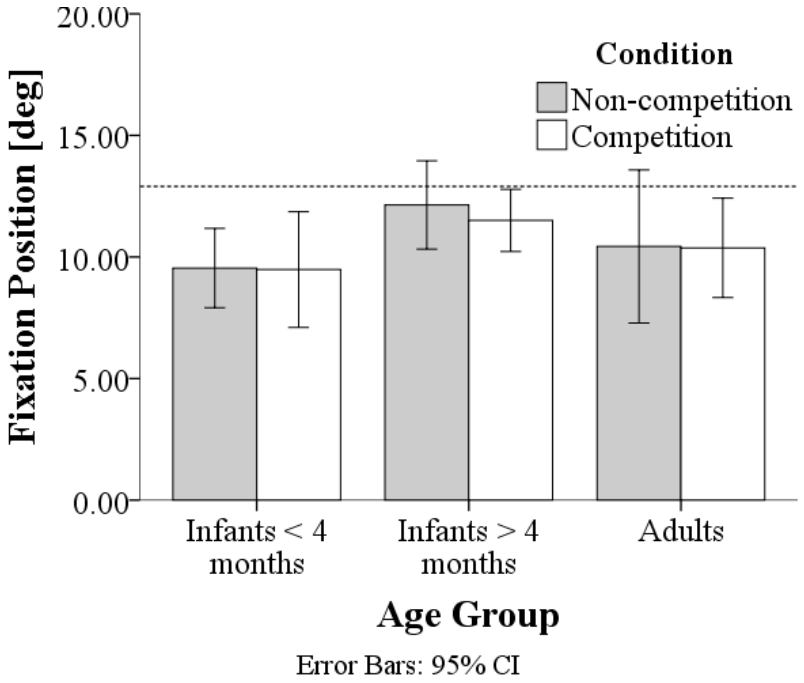


Figure E. 1. Gaze positions vary greater from the actual target position (dotted line) in infants younger than 4 months than in older infants and adults.

Despite differences in head circumference between older infants and adults, their gaze positions did not differ significantly. This suggests that the differences in fixation position between infants under and over the age of 4 months are unlikely to be due to differences in the fit of the calibration, as in that case fixation positions should also differ between older infants and adults. Instead, it is more likely that young infants indeed undershoot the target, as suggested by Aslin and Salapatek (1975). This may be followed by corrective saccades, which could not be investigated in this study because the target stimulus disappeared after the first saccade towards it. Appendix B found the

spatial accuracy of the eye tracker to be 0.8 degree, demonstrating that the difference between infants can reliably detected with the current set up.

Appendix F: Plots of the neural responses in Chapter 4.

F.1. Raw responses

Response amplitudes are colour coded on a scale from -2µV (blue) to 2 µV (red).

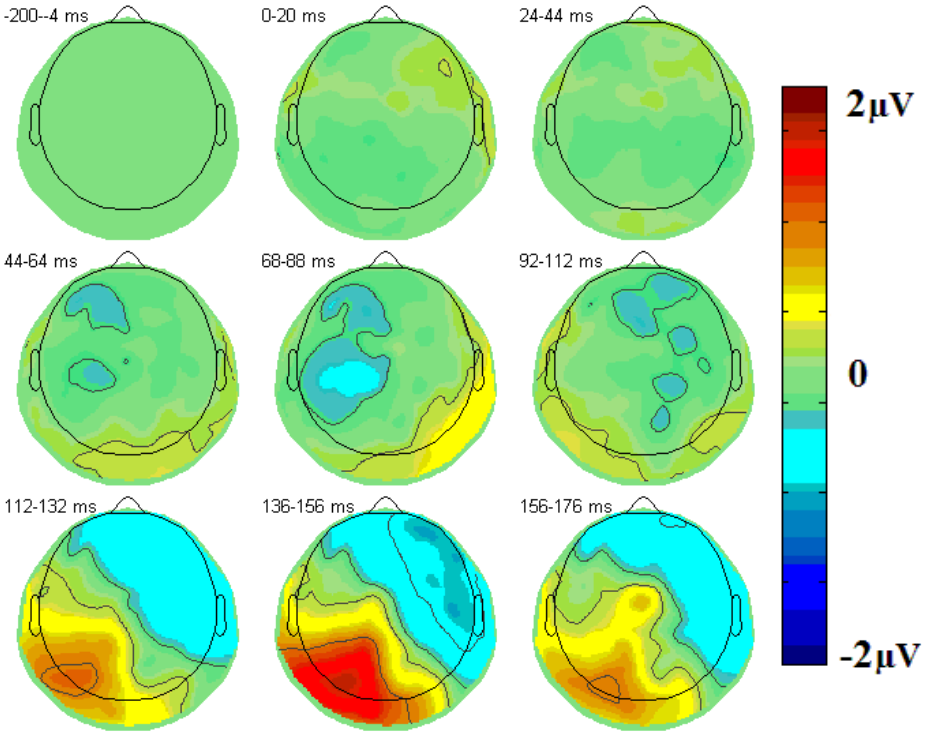


Figure F.1. 1. Topographical plots of the response to **single left** targets for **saccades**.

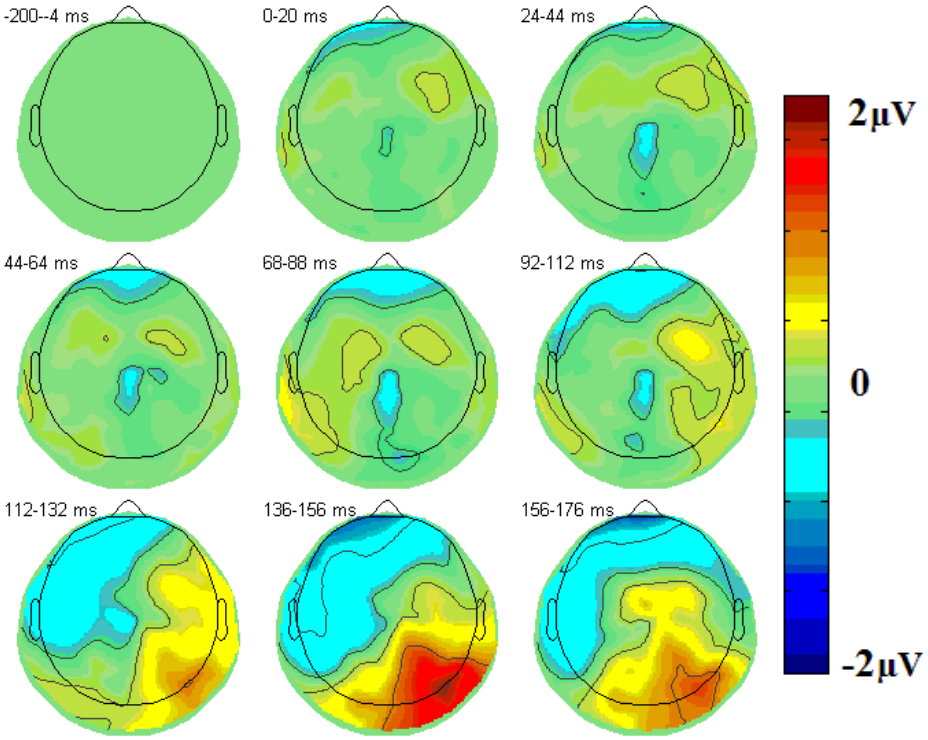


Figure F.1. 2. Topographical plots of the response to **single right** targets for **saccades**.

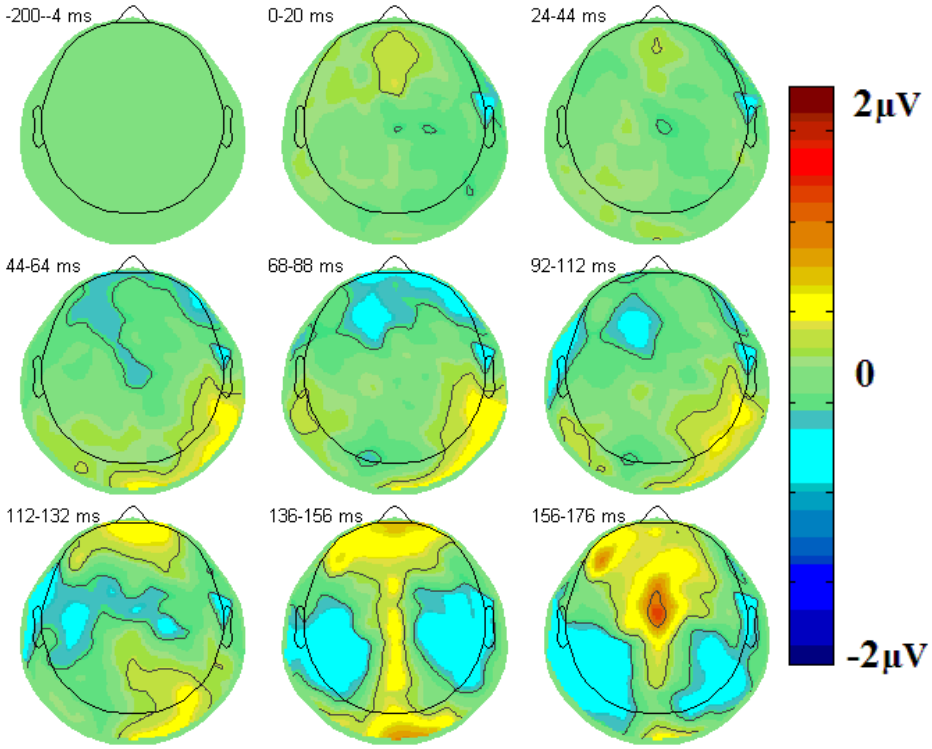


Figure F.1. 3. Topographical plots of the response for **saccades** in the **double target** condition when subjects subsequently looked towards the **left** target.

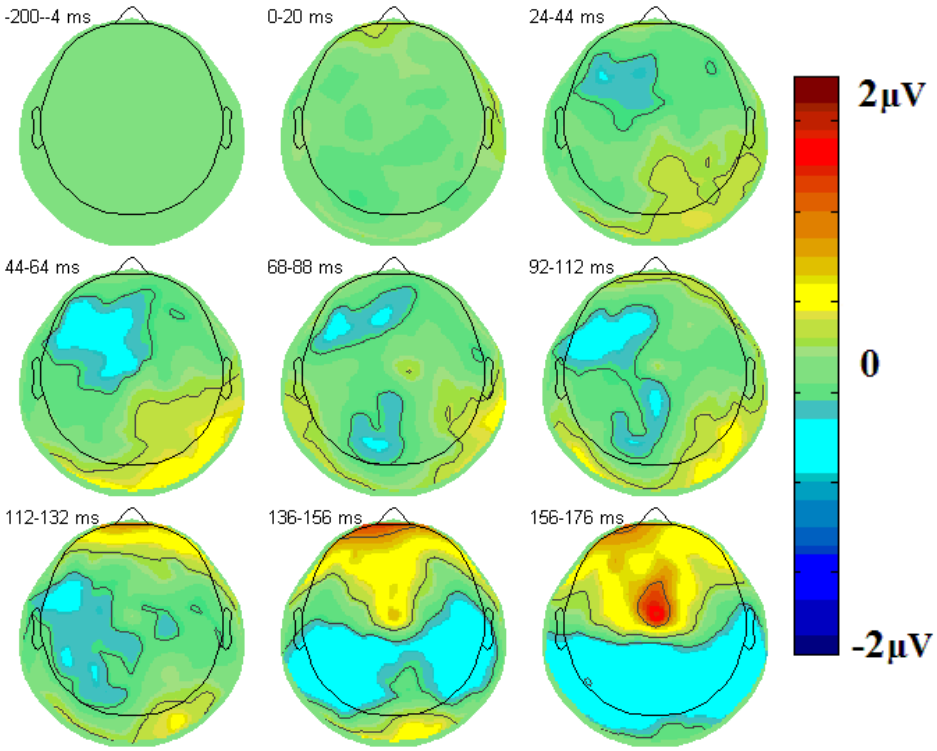


Figure F.1. 4. Topographical plots of the response for **saccades** in the **double target** condition when subjects subsequently looked towards the **right** target.

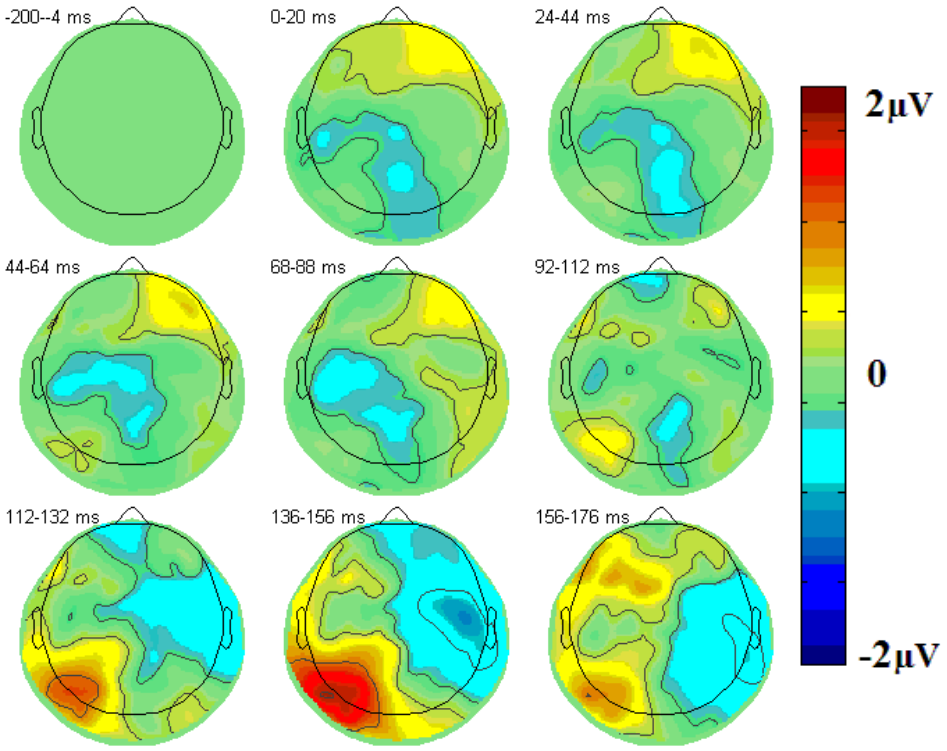


Figure F.1. 5. Topographical plots of the response to **single left** targets in **manual response** conditions.

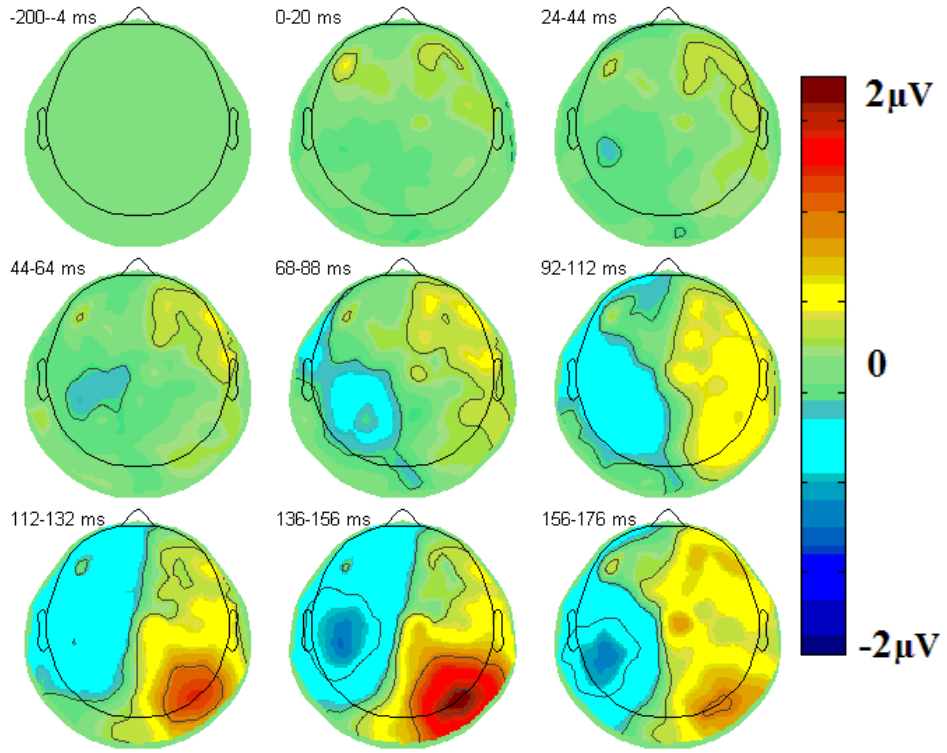


Figure F.1. 6. Topographical plots of the response to **single right** targets in **manual response** conditions.

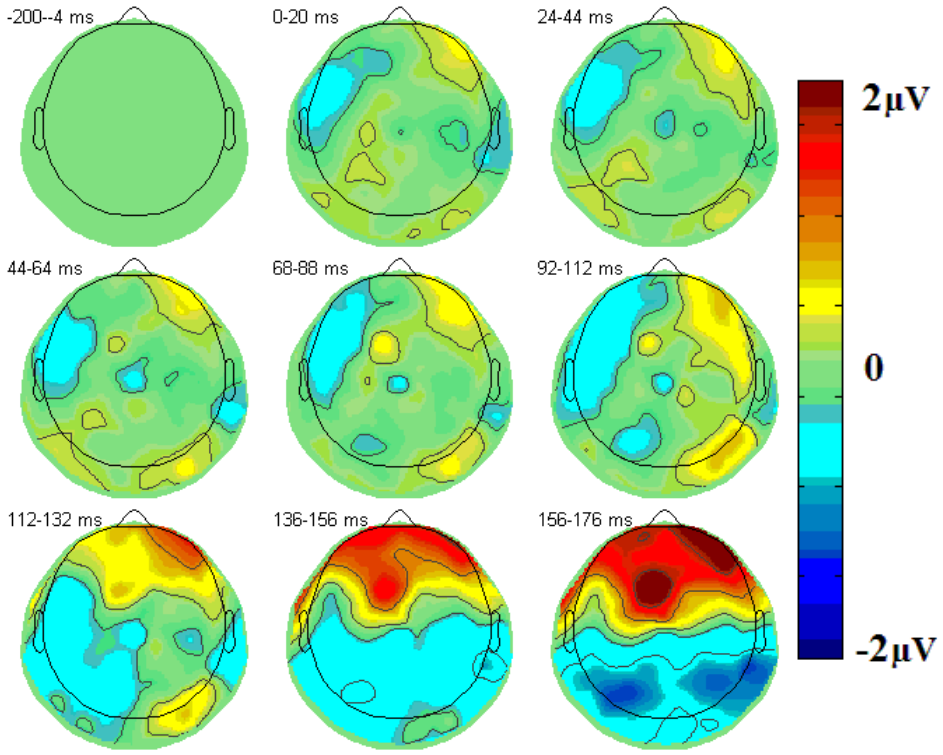


Figure F.1. 7. Topographical plots of the response in **manual double target** conditions when subjects subsequently pressed the **left** button.

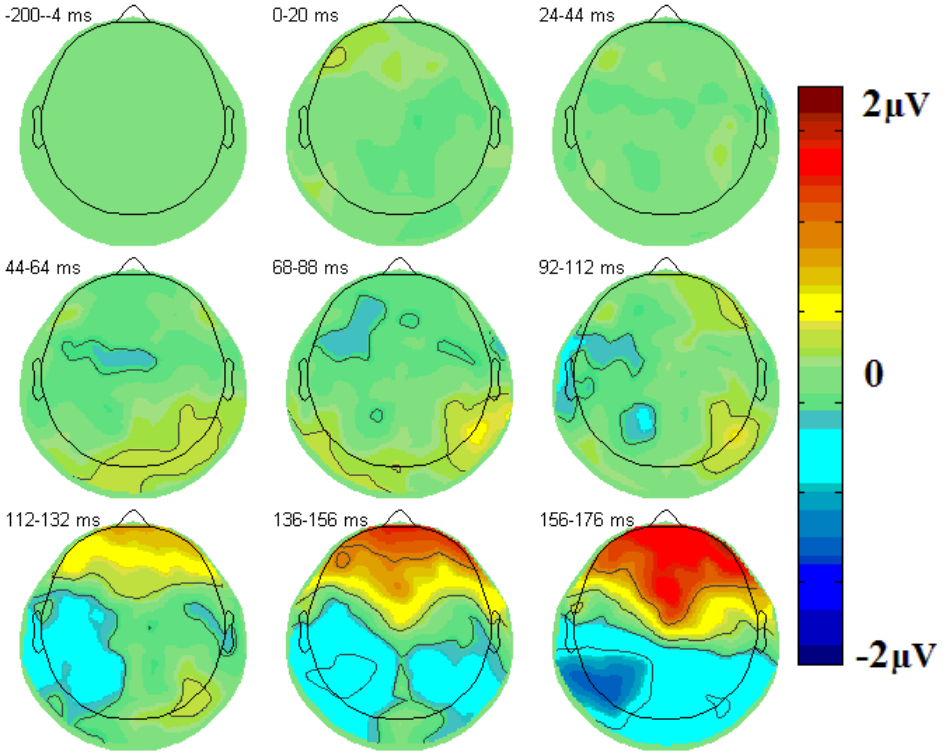
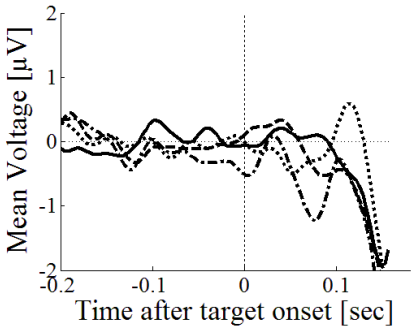


Figure F.1. 8. Topographical plots of the response in **manual double target** conditions when subjects subsequently pressed the **right** button.

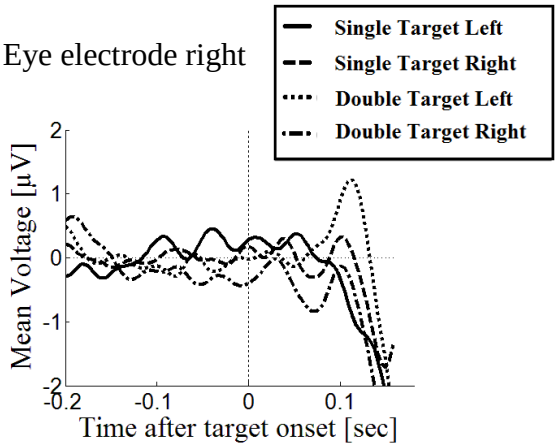
Wave plots

Saccade conditions: These wave plots display responses in saccade conditions for eye electrodes (top), prefrontal, frontal and central electrode locations.

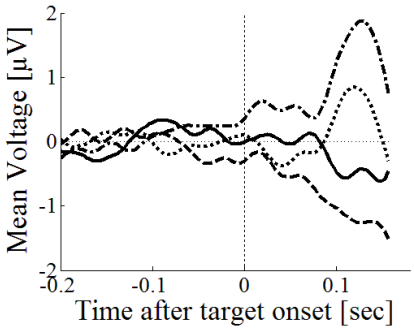
Eye electrode left



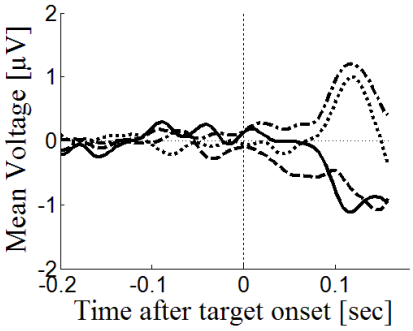
Eye electrode right



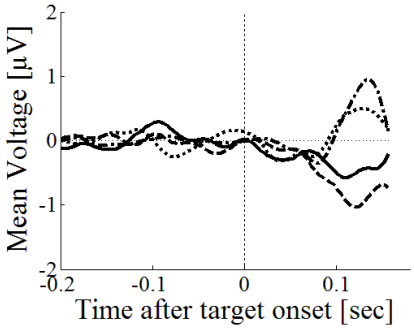
Prefrontal electrode left (FP1, E22)



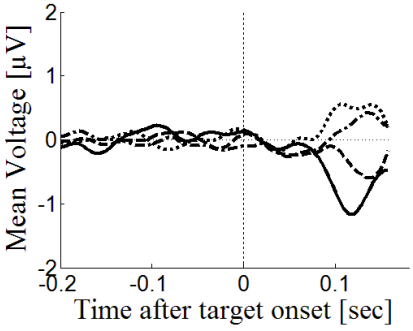
Prefrontal electrode right (FP2, E9)



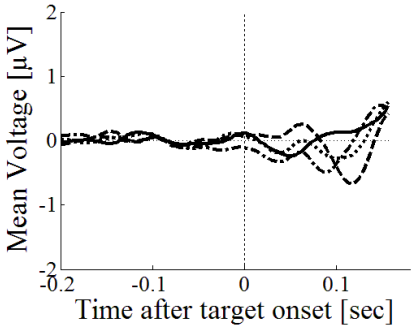
Frontal electrode left (F1, E19)



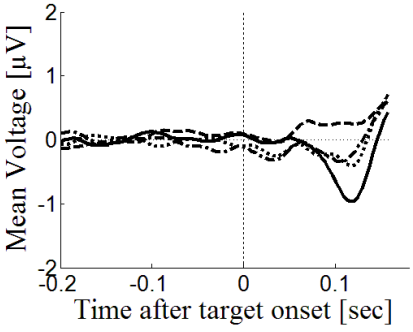
Frontal electrode right (F2, E4)



Central electrode left (C1, E30)



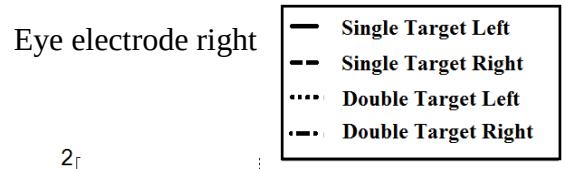
Central electrode right (C2, E105)

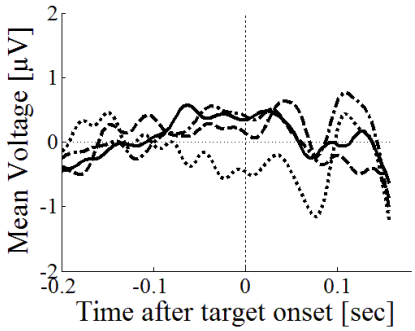


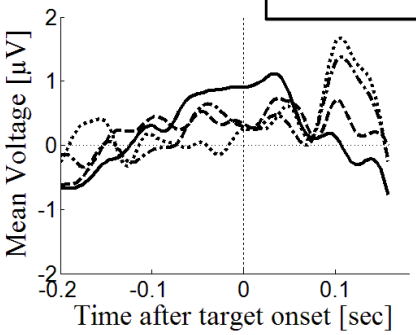
Manual response conditions: These wave plots display responses in manual conditions for eye electrodes (top), prefrontal, frontal and central electrode locations.

Eye electrode left

Eye electrode right

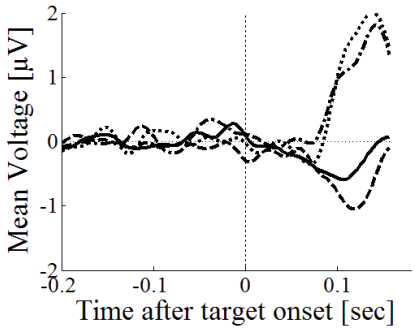


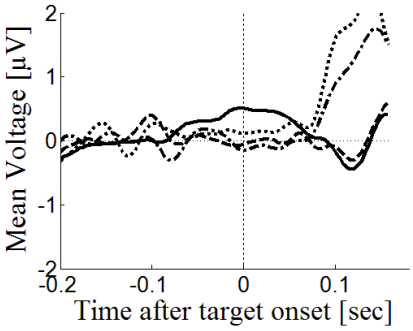




Prefrontal electrode left (FP1, E22)

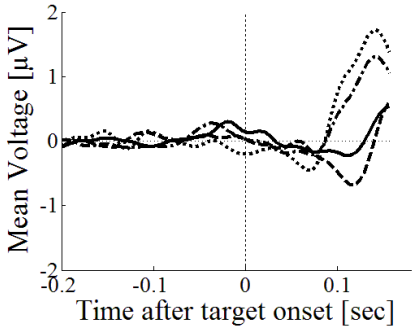
Prefrontal electrode right (FP2, E9)

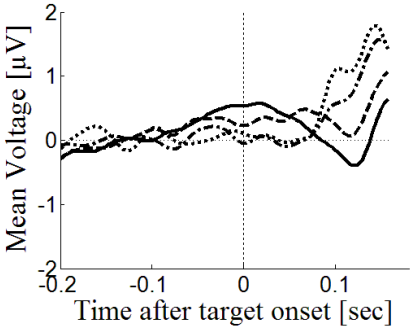




Frontal electrode left (F1, E19)

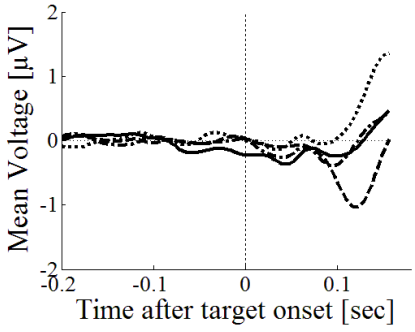
Frontal electrode right (F2, E4)

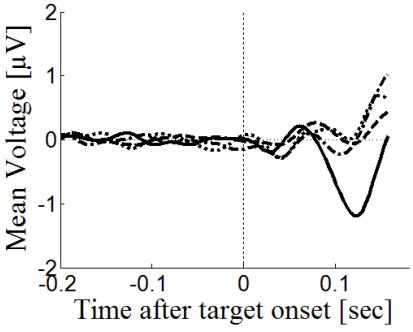




Central electrode left (C1, E30)

Central electrode right (C2, E105)





F.2. Difference between responses in saccade and manual response conditions.

Response amplitudes are colour coded on a scale from -2µV (blue) to 2 µV (red).

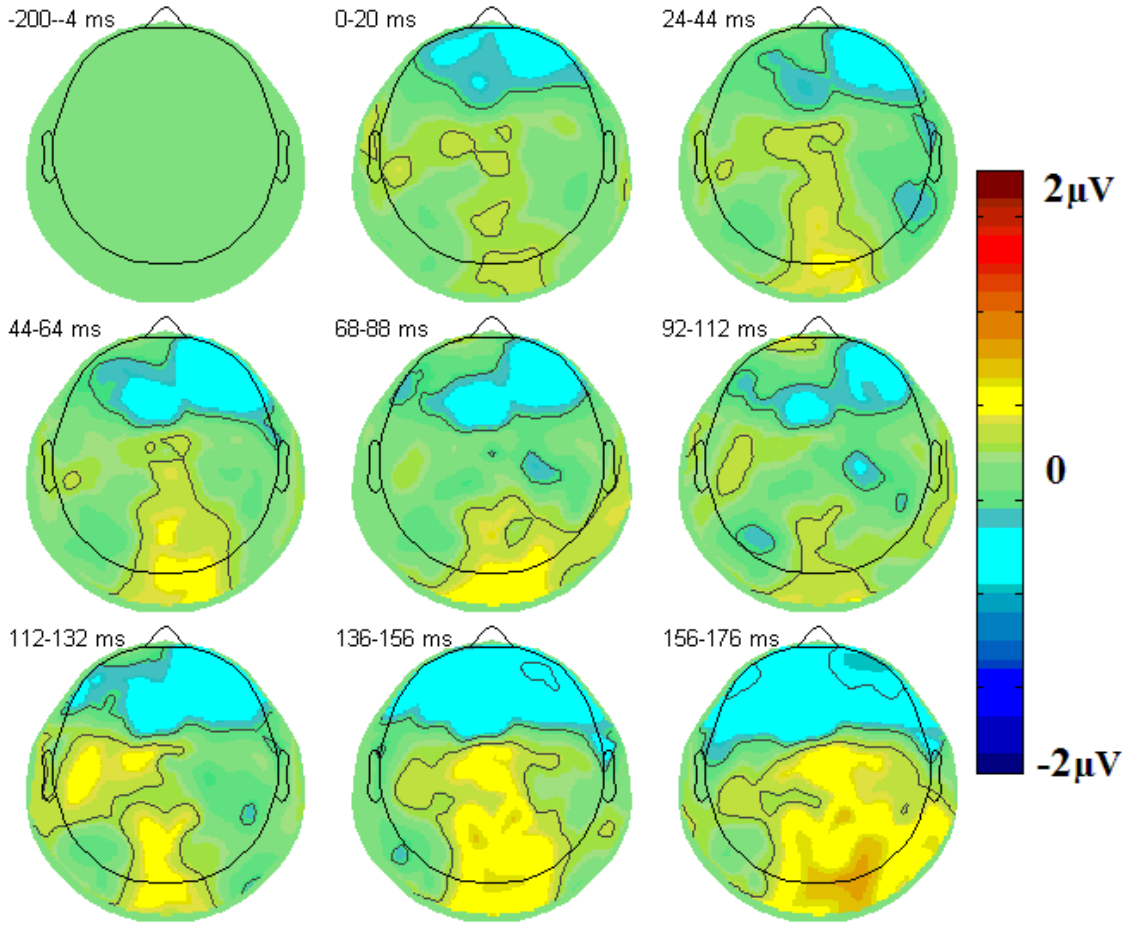


Figure F.2. 1. Difference response between **saccade conditions minus manual response conditions** for **single** targets on the **left** side of the screen.The plot shows that posterior responses are more positive, particularly on the contralateral side, and last longer for saccades, while the frontal positivity is stronger for manual responses (hence the negativity towards the end of the extracted time window).

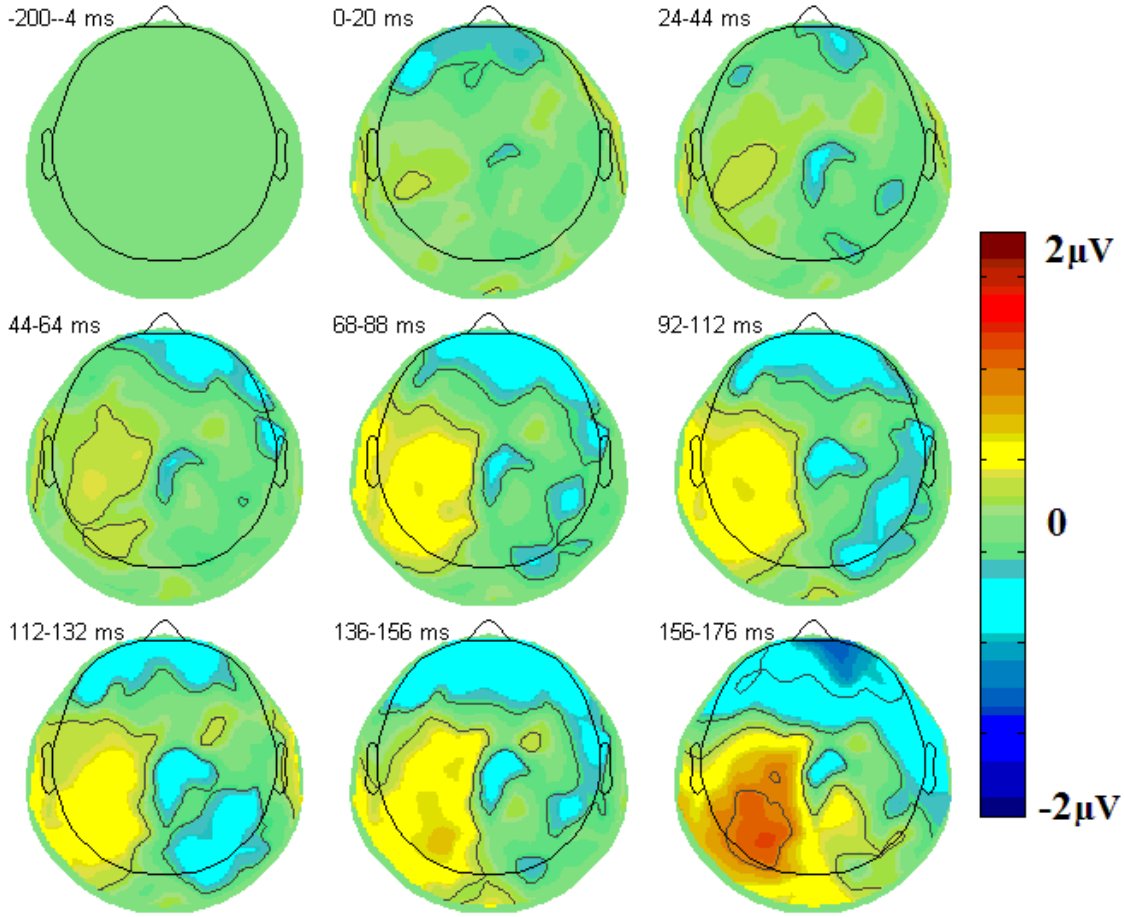


Figure F.2. 2. Difference response between **saccade conditions minus manual response conditions** for **single** targets on the **right** side of the screen. The plot shows that posterior responses are more positive for saccades, particularly on the contralateral side, and last longer for saccades, while the frontal positivity is stronger for manual responses (hence the negativity towards the end of the extracted time window).

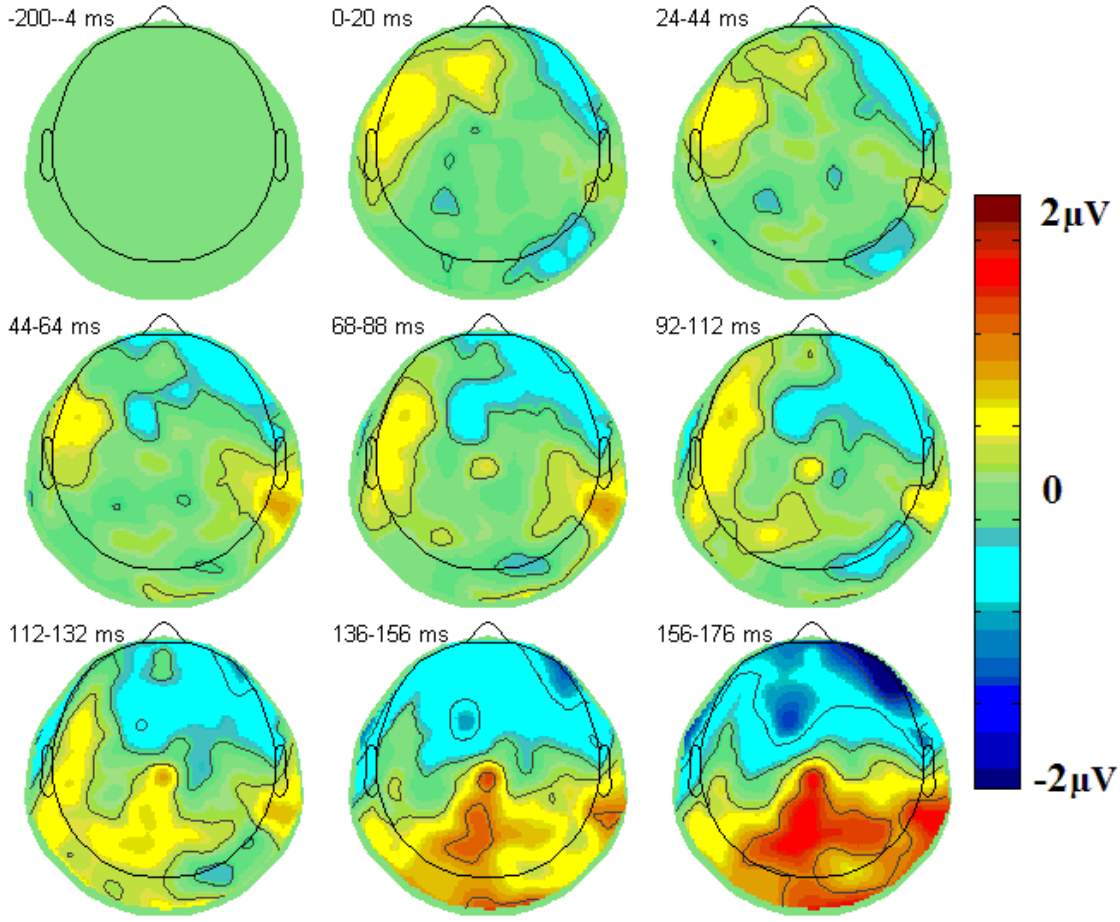


Figure F.2. 3. Difference response between **saccade conditions minus manual conditions** for **double** targets on the **left** side of the screen. Posterior responses are more positive and last longer in saccade conditions, while the frontal positivity is greater in manual conditions.

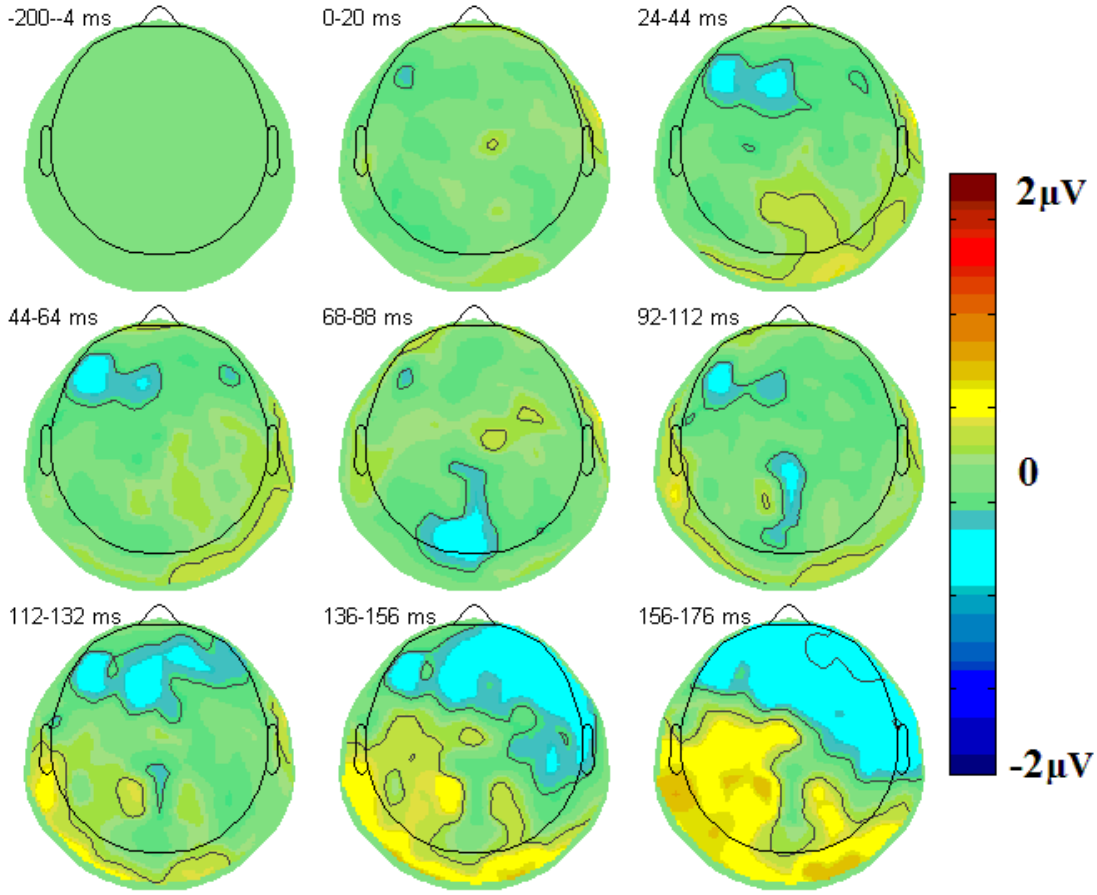


Figure F.2. 4. Difference response between **saccade conditions minus manual conditions** for **double** targets on the **right** side of the screen. Posterior responses are more positive and last longer in saccade conditions, while the frontal positivity is greater in manual conditions.

Appendix G. Topographical plots of responses in Chapter 5, Study 1.

Response amplitudes are colour coded on a scale from -2μV (blue) to 2μV (red).

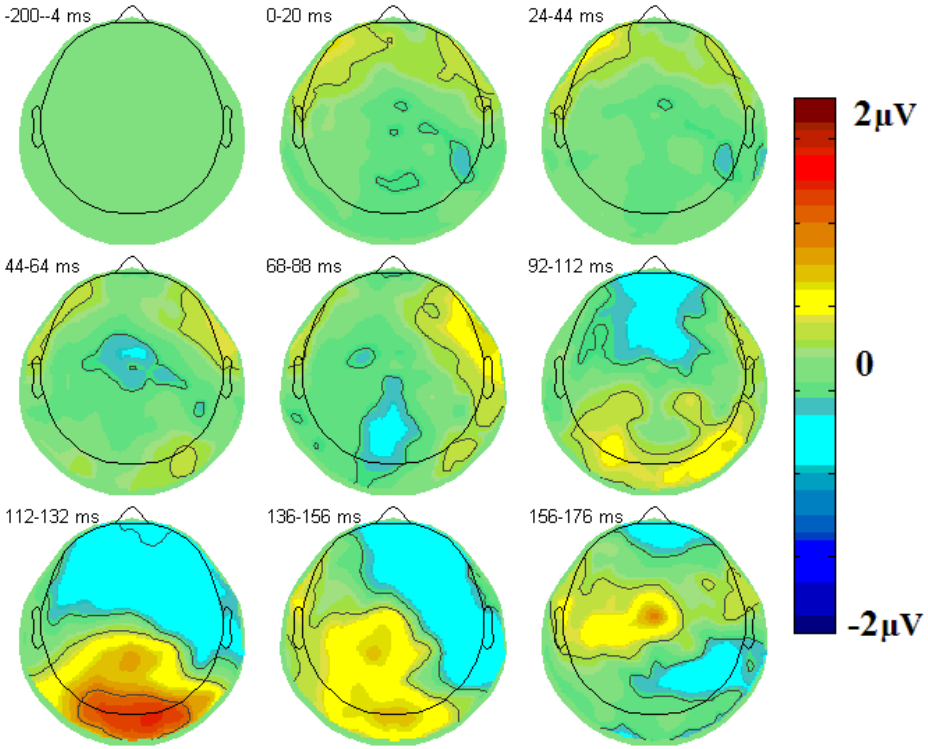


Figure G. 1. Topographical plots of the brain response to **single** targets on the **left** side in **non-competition** conditions.

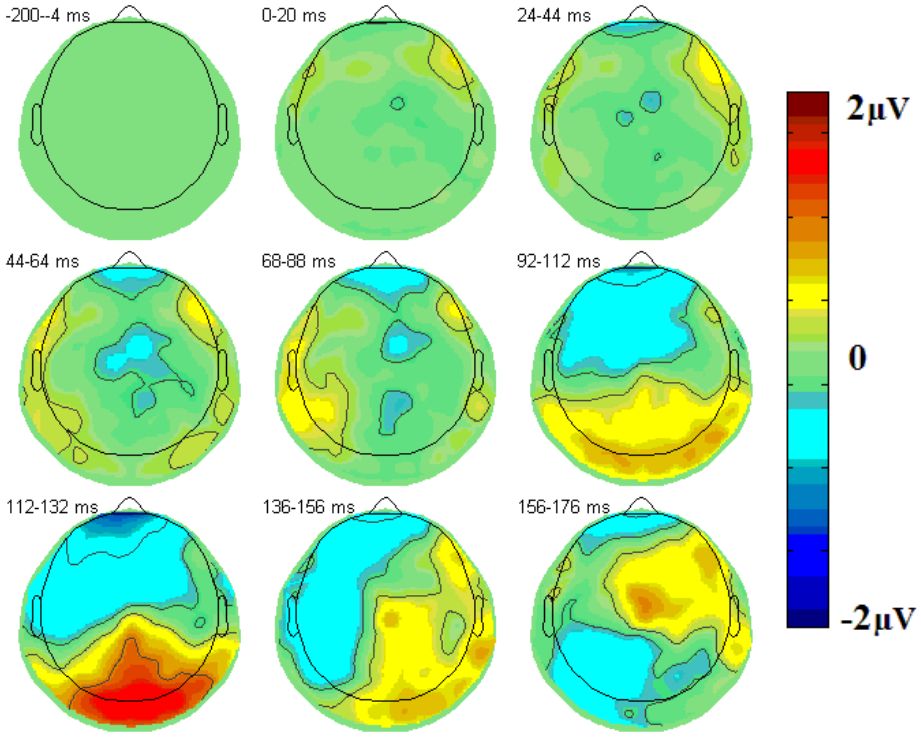


Figure G. 2. Topographical plots of the brain response to **single** targets on the **right** side in **non-competition** conditions.

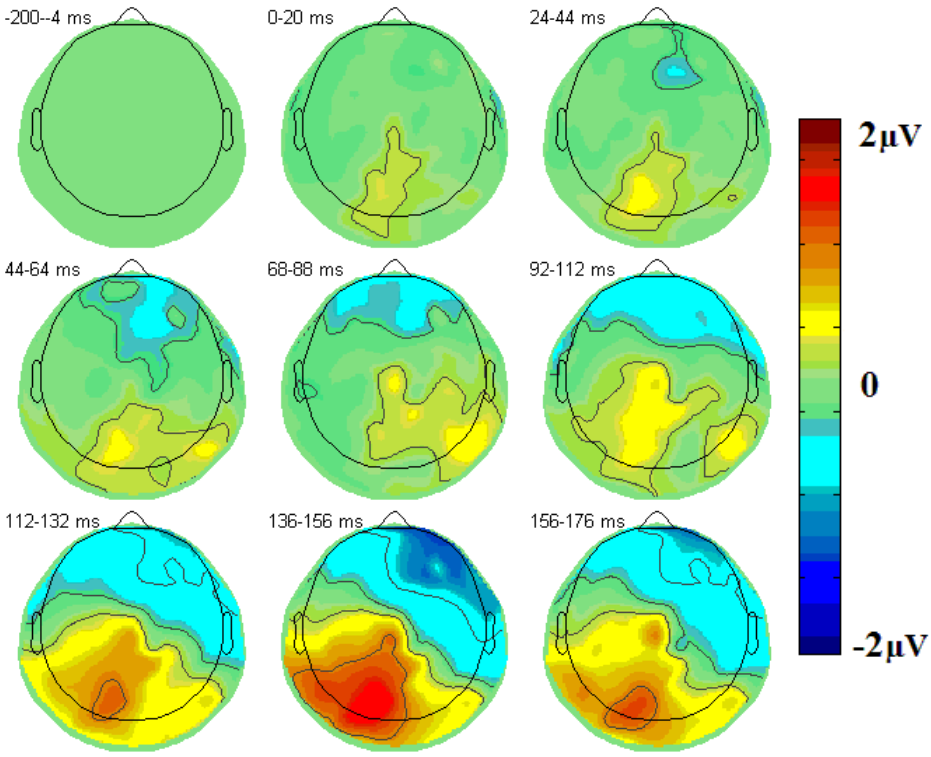


Figure G. 3. Topographical plots of the brain response to **single** targets on the **left** side in **competition** conditions.

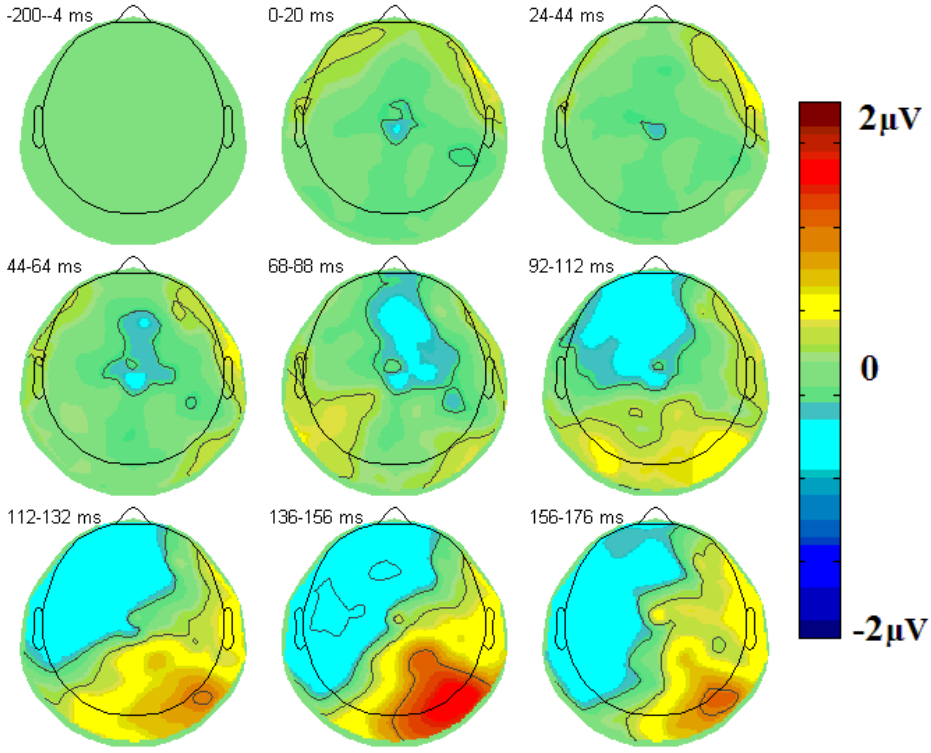


Figure G. 4. Topographical plots of the brain response to **single** targets on the **right** side in **competition** conditions.

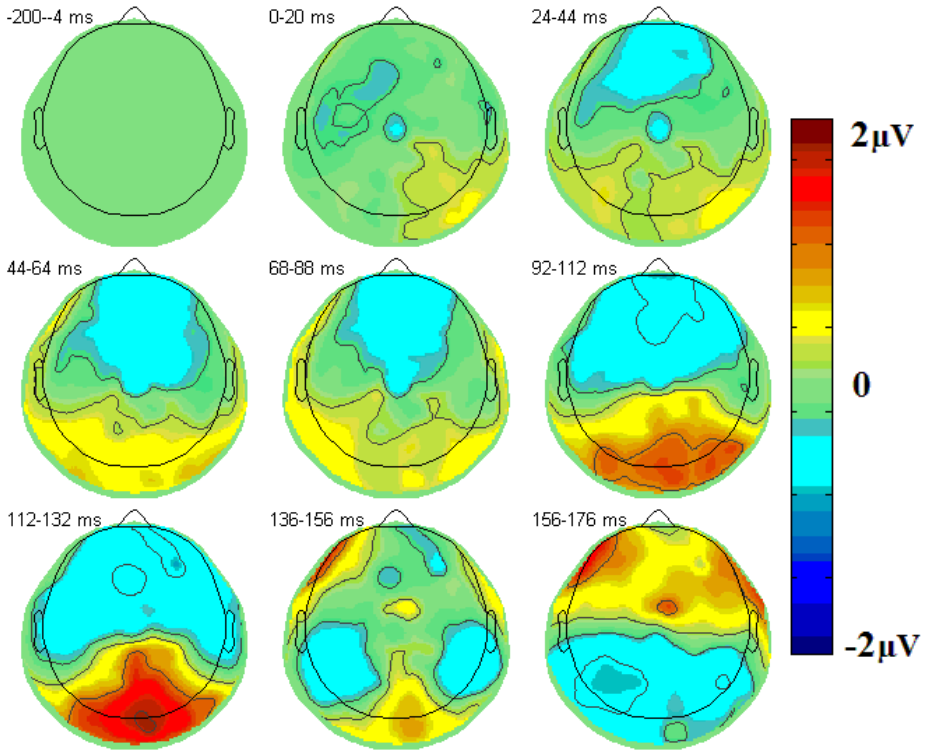


Figure G. 5. Topographical plots of the brain response to **double** targets in **non-competition** conditions when saccades were executed towards targets on the **left** side.

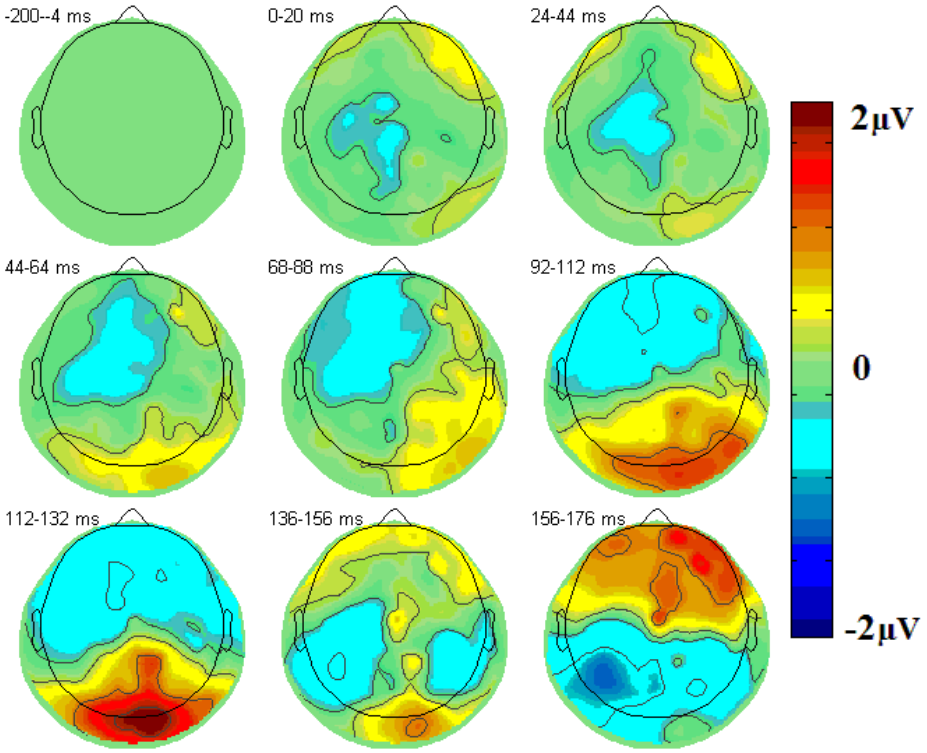


Figure G. 6. Topographical plots of the brain response to **double** targets in **non-competition** conditions when saccades were executed towards targets on the **right** side.

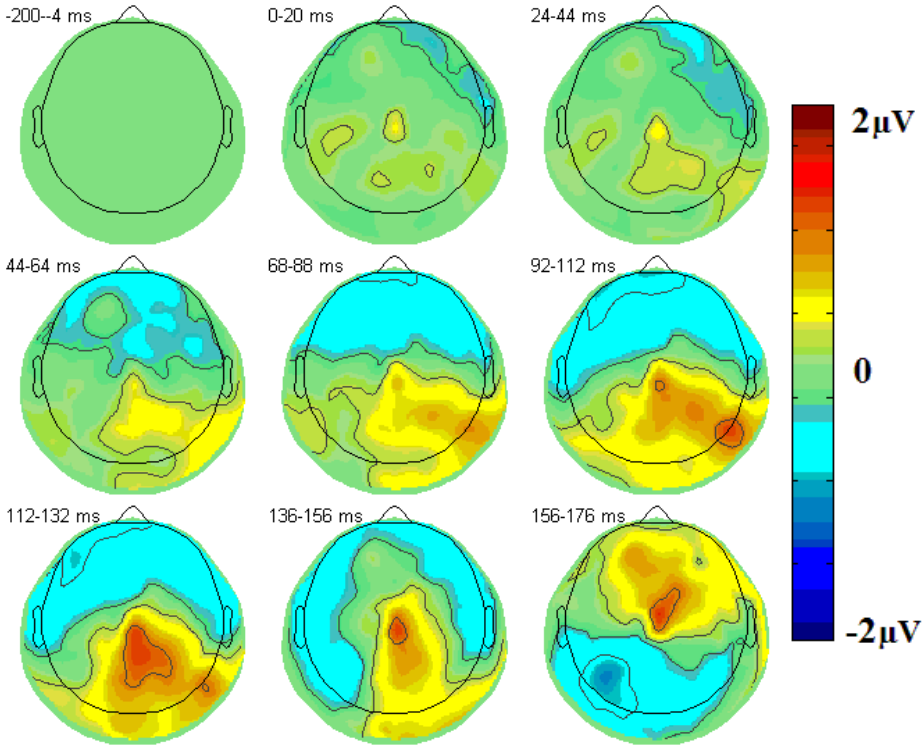


Figure G. 7. Topographical plots of the brain response to **double** targets in **competition** conditions when saccades were executed towards targets on the **left** side.

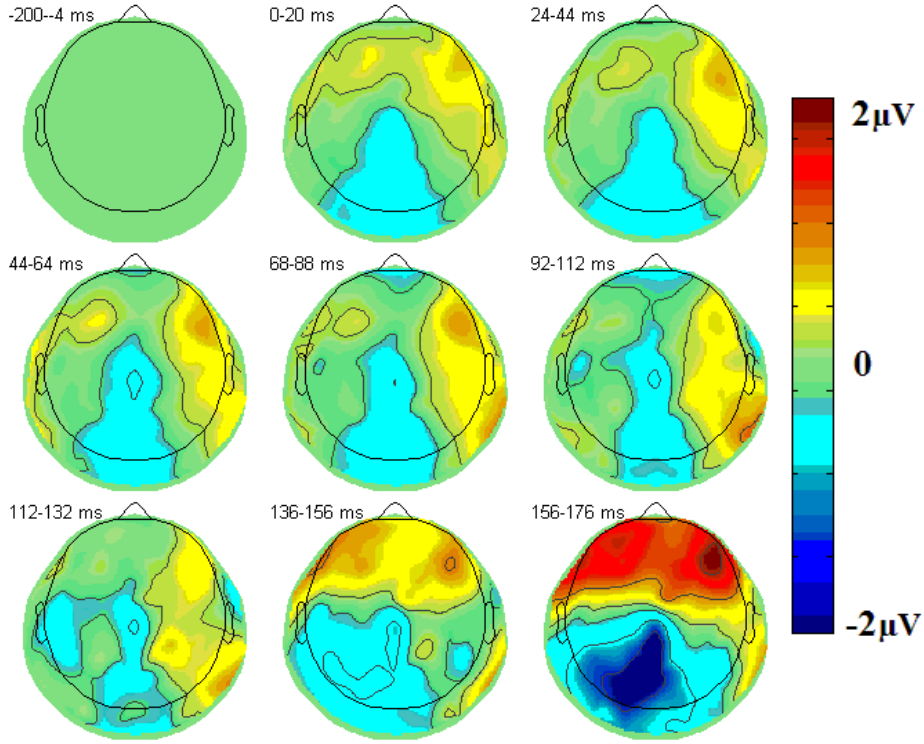


Figure G. 8. Topographical plots of the brain response to **double** targets in **competition** conditions when saccades were executed towards targets on the **right** side.

Appendix H. Topographical plots of responses in Chapter 5, Study 2.

Responses are colour coded on a scale from -2μV (blue) to 2μV (red).

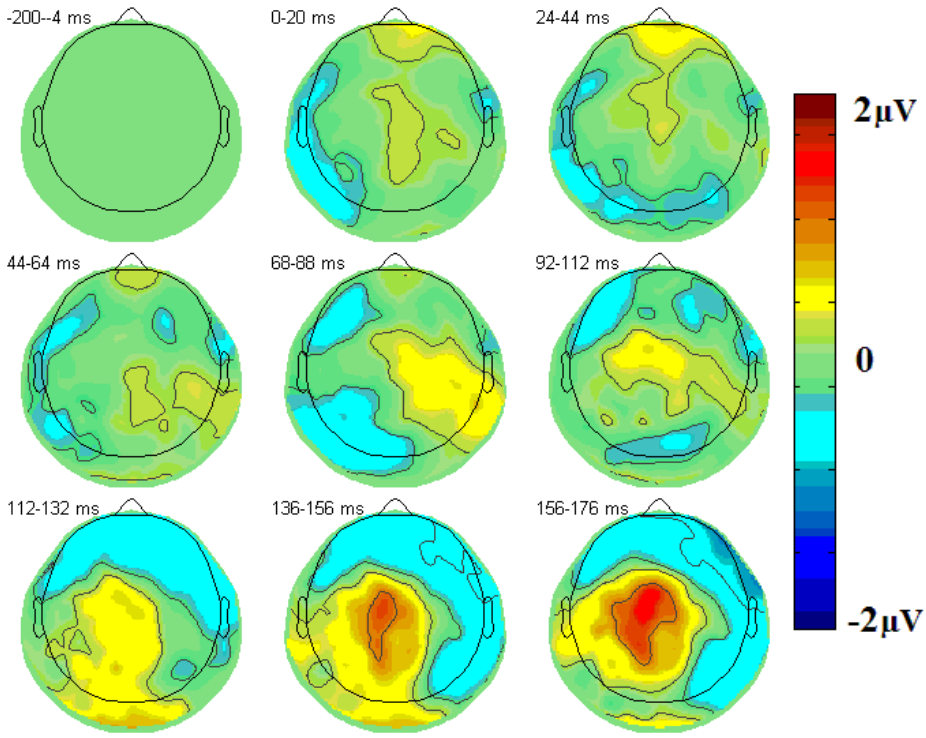


Figure H. 1. Topographical plots of responses to stimuli on the **left** side of the screen in **non-competition** conditions.

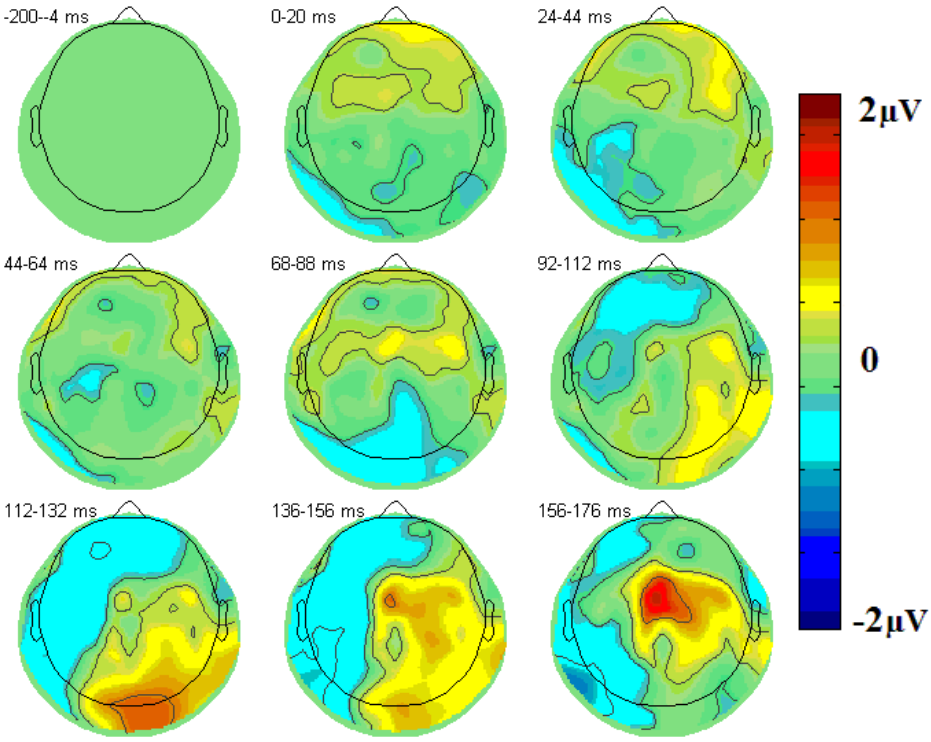


Figure H. 2. Topographical plots of responses to stimuli on the **right** side of the screen in **non-competition** conditions.

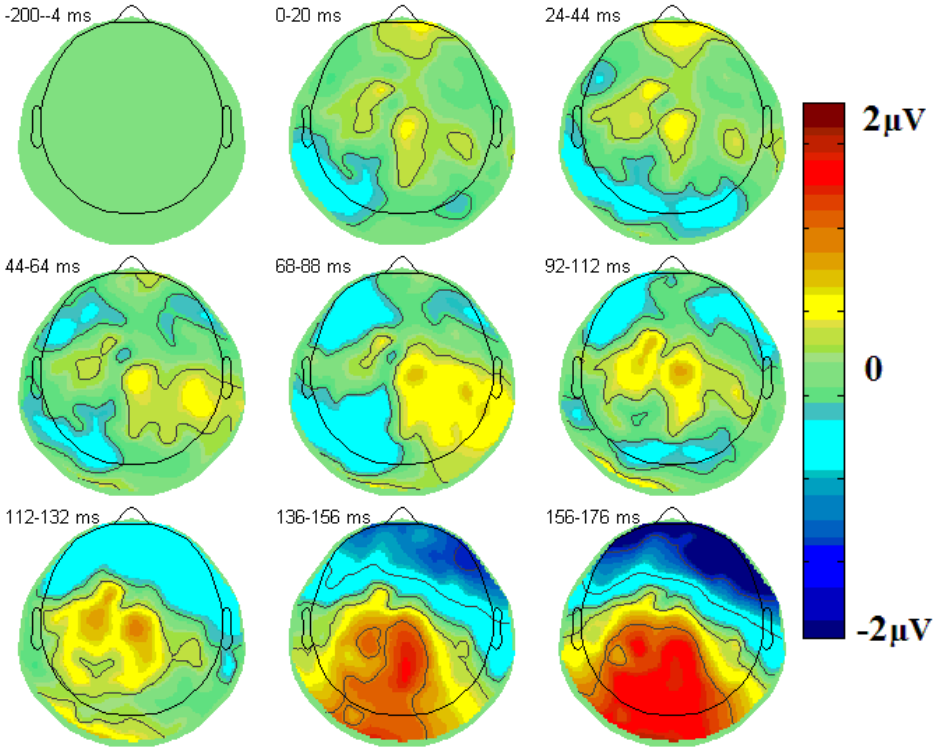


Figure H. 3. Topographical plots of the **difference** response of conditions with stimuli on the **left** side of the screen minus the offset response.

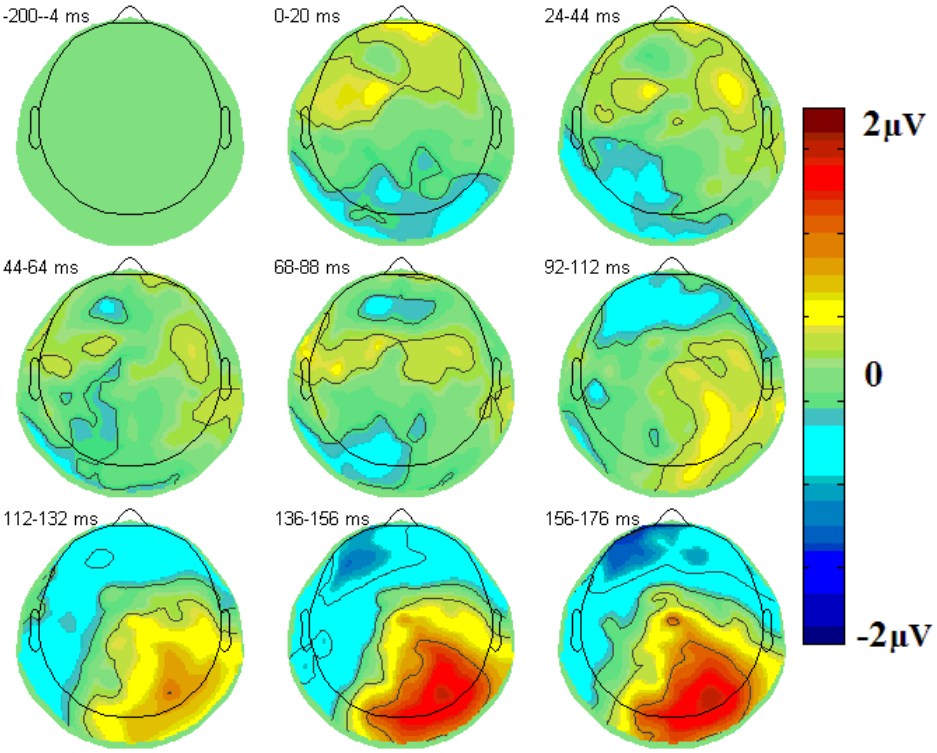


Figure H. 4. Topographical plots of the **difference** response of conditions with stimuli on the **right** side of the screen minus the offset response.

Appendix I. Behavioural results including all infants from Chapter 6

As behavioural data is less noisy than EEG data, the analysis was repeated including all infants tested for the study, also the ones who did not meet strict minimum trial numbers for EEG analysis (> 5 trials per condition, see Chapter 6, section 6.2.1).

Data quality

In the whole group of infants, 77.3% of trials were correct re-fixations, 3.2% were sticky fixations, 8.1% of saccades went to the wrong direction, 5.4% were wrong but subsequently corrected and 11.3% of trials were noisy data.

Sticky fixations

Mixed logistic regressions including participants as random effect and condition, age group and number of stimuli as fixed factors showed a significant effect of condition on the proportion of sticky fixations, $z = 4.36$, $p < .001$, with less sticky fixations in the non-competition ($M = 1.2\%$, $SD = 10.7\%$), than in the competition condition ($M = 5.1\%$, $SD = 22.1\%$), a significant effect of age group, $z = -2.69$, $p = .007$, with decreasing proportions of sticky fixations with age (Table I.1). There was furthermore a significant interaction of condition and age group, $z = -3.43$, $p < .001$, showing decreasing proportions of sticky fixations with age in the non-competition condition (Figure I.1). There was no significant effect of number of stimuli, $z = -0.09$, $p = .926$ and no significant interactions with stimulus number.

Table I. 1. *Means and standard deviations of the percentages of sticky fixations in different age groups.*

Age group	M	SD
1.5-2.5	5.68%	23.2%
2.5-3.5	3.22%	17.7%
3.5-5.5	1.47%	12.1%
5.5-7.5	0.99%	9.9%

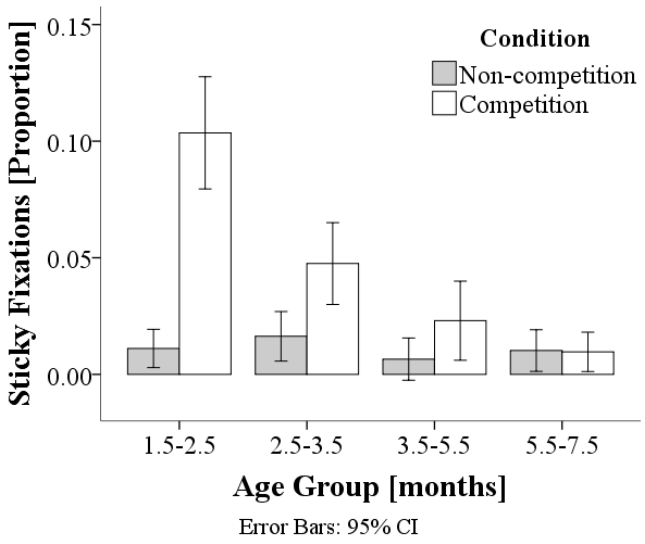


Figure I. 1. Interaction effect of age and condition on the proportion of sticky fixations. Sticky fixations in the competition condition decrease with age.

Mixed logistic regressions were repeated to investigate differences in noisy data between groups. There was a significant effect of age group, $z = 2.11$, $p = .035$, showing an increase in noisiness with age (Figure I.2), and a significant interaction of age group and condition, $z = 2.50$, $p = .013$, showing that the increase with age mainly occurred in the competition condition. There was also a significant interaction of condition and number of stimuli, $z = 2.07$, $p = .038$, showing that higher proportions of noise in the competition condition only occurred for double but not for single targets (Figure I.3).

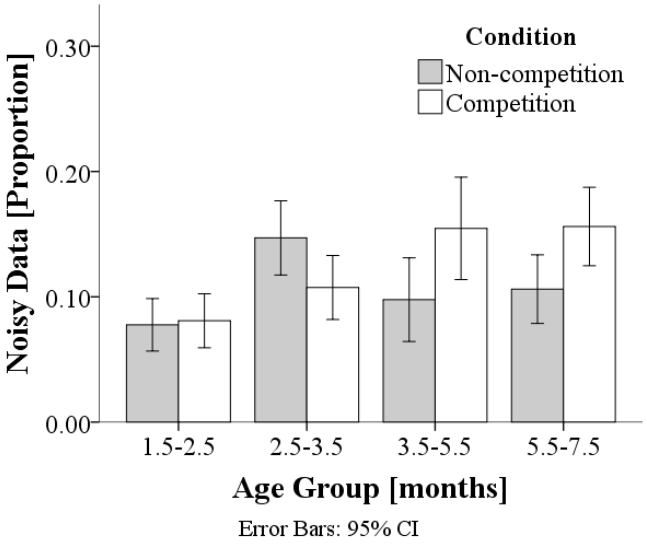


Figure I. 2. The proportion of noisy data increases with age, particularly in the competition condition.

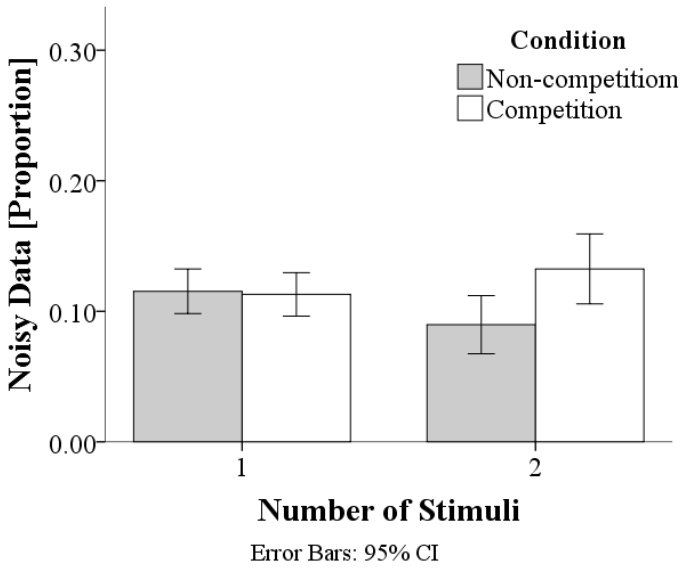


Figure I. 3. Higher proportions of noise in the competition condition only occur for double but not for single targets.

Saccade latency

To investigate differences in saccade latencies between conditions, a linear mixed model was computed, including participants as random effects and condition (non-competition or competition), number of stimuli (1 or 2), screen side watched (left or right) and age group (1.5-2.5, 2.5-3.5, 3.5-5.5 or 5.5-7.5 months) as fixed factors.

There were significant main effects of condition, $F(1, 3008) = 149.03$, $p < .001$, $d = 0.474$, with shorter latencies in the non-competition ($M = 545$, $SD = 486$) than in the competition condition ($M = 872$, $SD = 848$), age group, $F(3, 65) = 7.36$, $p < .001$, $d = 0.347$, with decreasing latencies with age (Table I.2), and number of stimuli, $F(1, 3009) = 13.21$, $p < .001$, $d = 0.119$, with shorter latencies to single ($M = 672$, $SD = 690$) than towards double targets ($M = 756$, $SD = 722$). There were significant interactions of age group and condition, $F(3, 3008) = 24.00$, $p < .001$, showing that latencies under competition decrease with age while latencies under non-competition remain fairly constant (Figure I.4), and a small three-way interaction of age group, condition and number of stimuli, $F(3, 2999) = 2.57$, $p = .052$, showing that latencies towards double targets ceased to differ between conditions at 5.5 months (Figure I.5). There was no bias towards one screen side, $F(1, 3035) = 1.64$, $p = .200$.

Table I. 2. *Saccade latencies (displayed in ms) significantly decrease with age, particularly between 1.5 and 5.5 months.*

Age group	*Mean*	*SD*
1.5-2.5 months	833	789
2.5-3.5 months	705	701
3.5-5.5 months	624	525
5.5-7.5 months	582	656

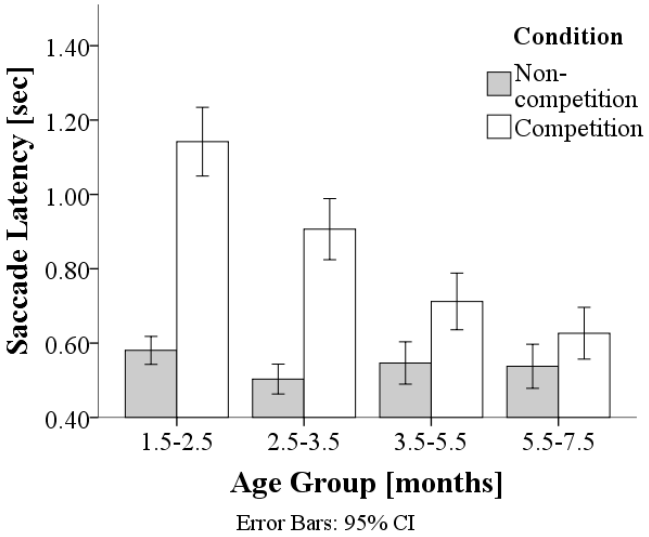


Figure I. 4. Interaction effect of age group and condition. Saccade latencies under competition decrease with age, while they stay at a lower but fairly constant level in the non-competition condition.

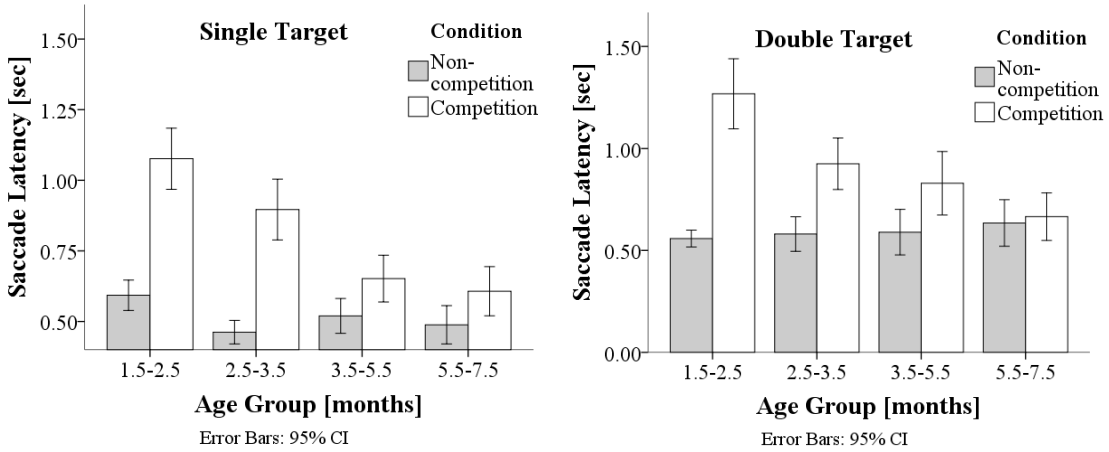


Figure I. 5. Three-way interaction of age group, condition and number of targets. Latencies decrease with age in competition, but not in non-competition conditions and the difference between conditions is greater for single targets.

Appendix J. Topographical plots of infant responses (Chapter 6)

Response amplitudes are visualised on a scale from -15 µV (blue) to 15 µV (red), averaged across infants who completed more than 5 successful trials per condition.

1.5-2.5 months

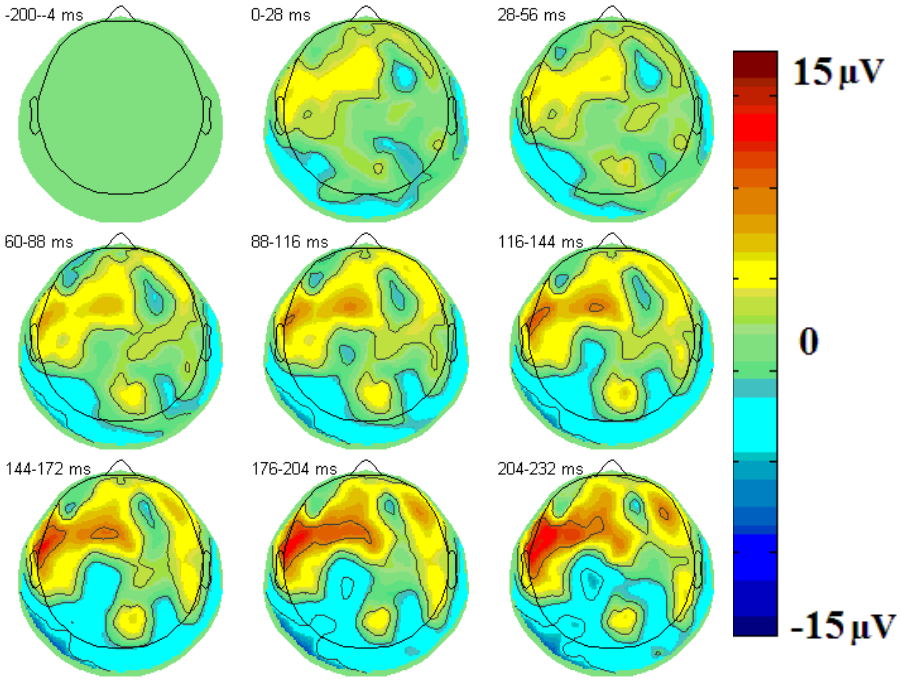


Figure J. 1. Topographical plots of the response to targets on the **left** side of the screen in **non-competition** conditions in infants between **1.5-2.5 months** of age.

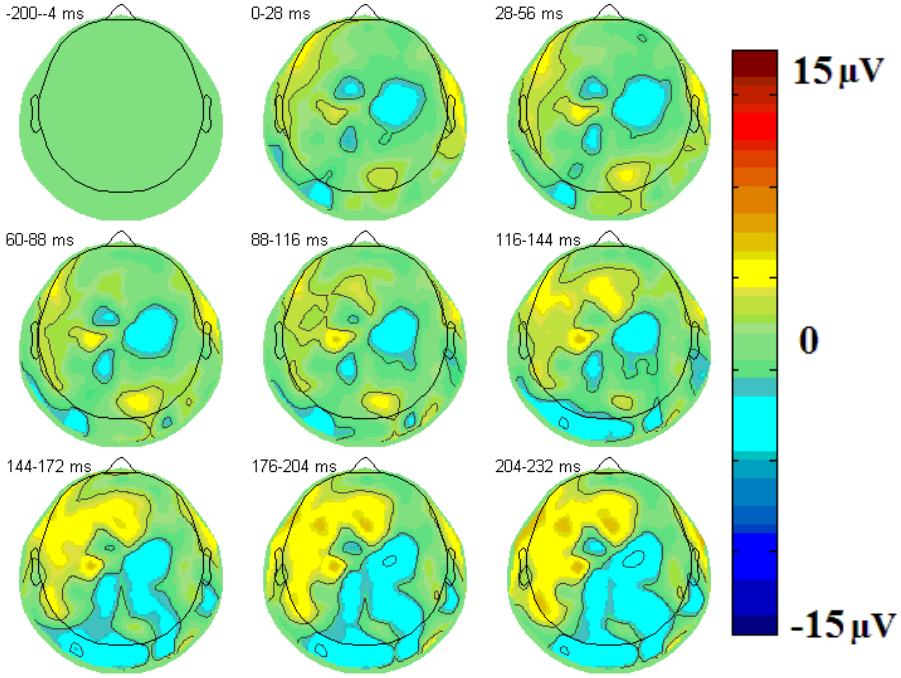


Figure J. 2. Topographical plots of the response to targets on the **right** side of the screen in **non-competition** conditions in infants between **1.5-2.5 months** of age.

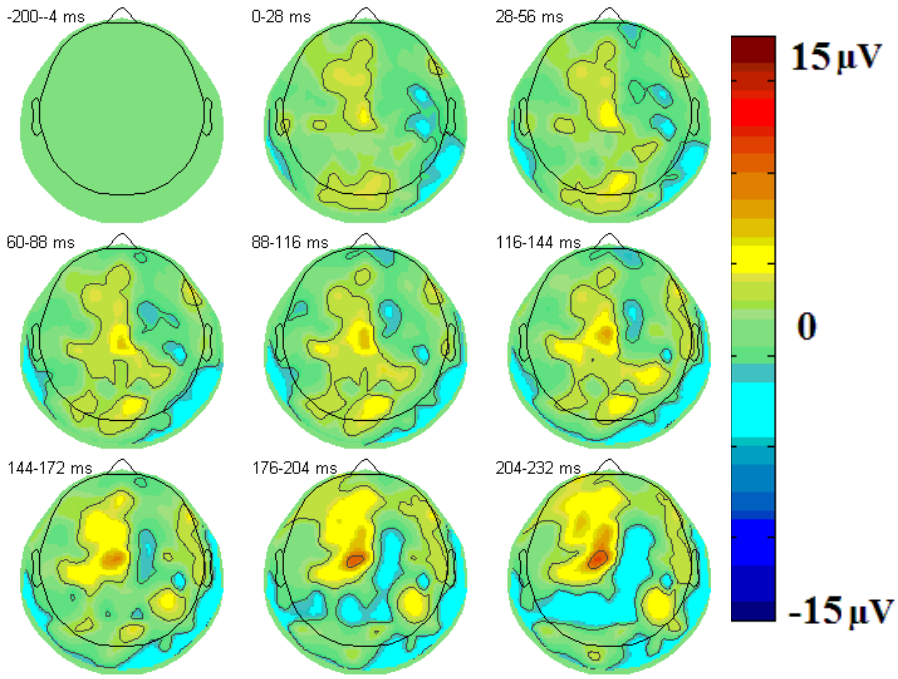


Figure J. 3. Topographical plots of the response to targets on the **left** side of the screen in **competition** conditions in infants between **1.5-2.5 months** of age.

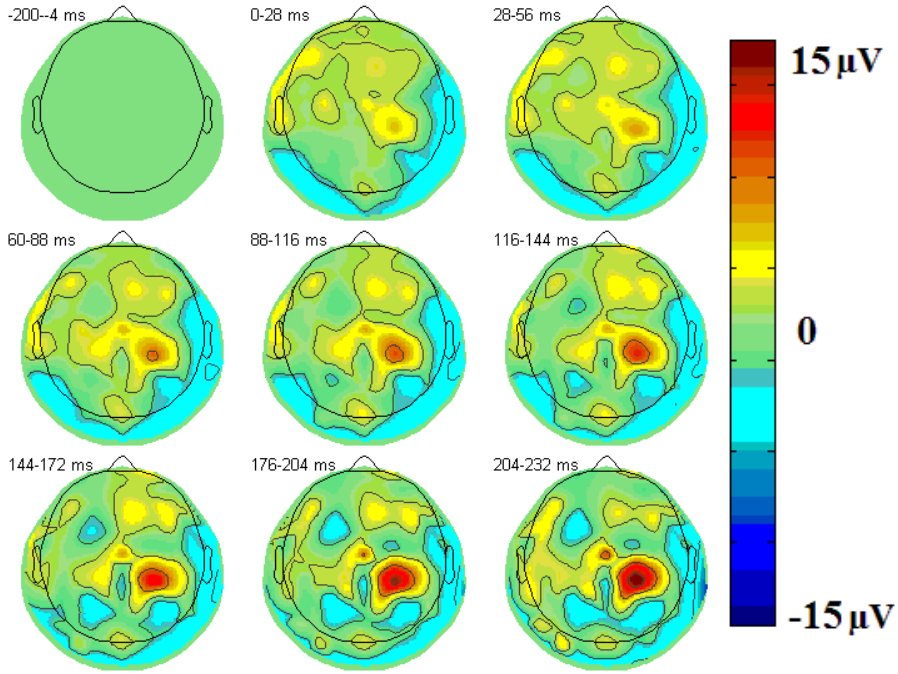


Figure J. 4. Topographical plots of the response to targets on the **right** side of the screen in **competition** conditions in infants between **1.5-2.5 months** of age.

2.5-3.5 months

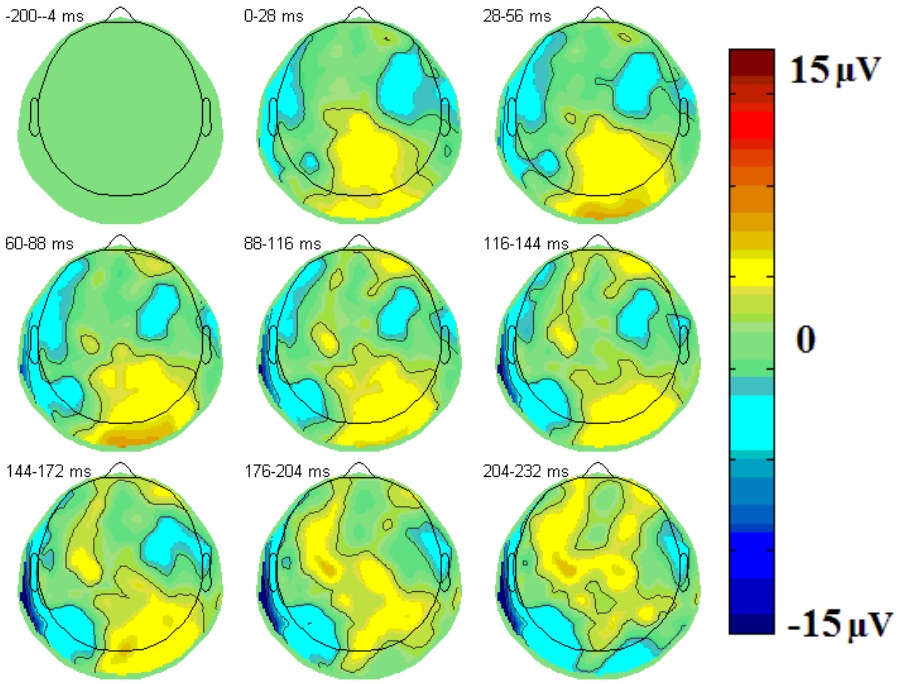


Figure J. 5. Topographical plots of the response to targets on the **left** side of the screen in **non-competition** conditions in infants between **2.5-3.5 months** of age.

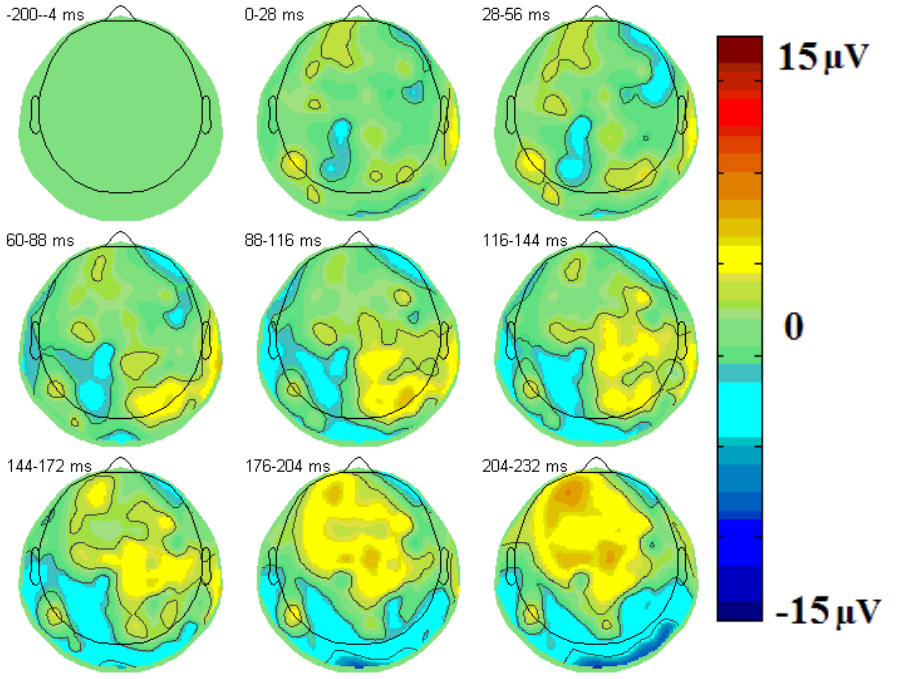


Figure J. 6. Topographical plots of the response to targets on the **right** side of the screen in **non-competition** conditions in infants between **2.5-3.5 months** of age.

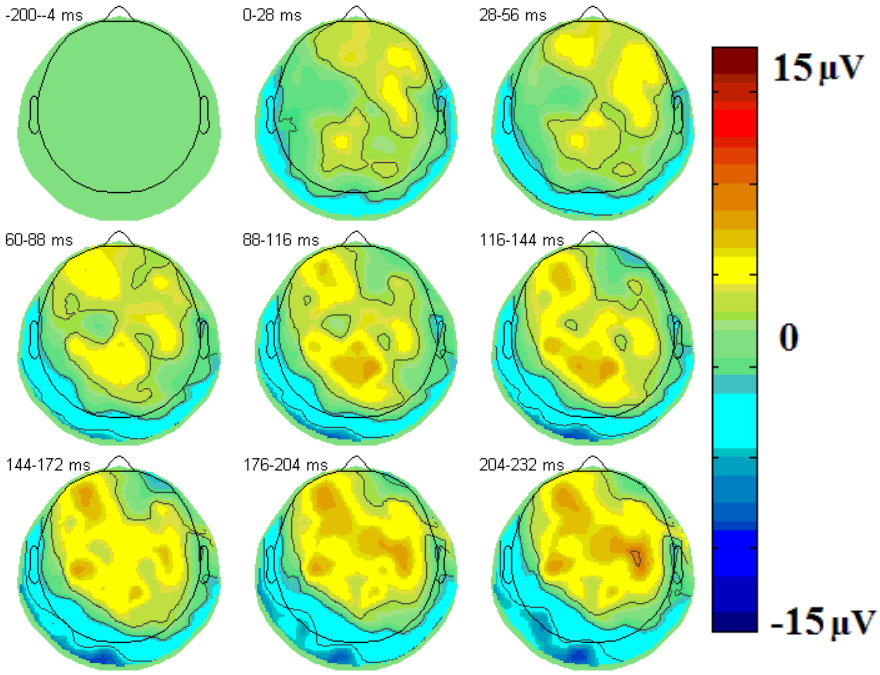


Figure J. 7. Topographical plots of the response to targets on the **left** side of the screen in **competition** conditions in infants between **2.5-3.5 months** of age.

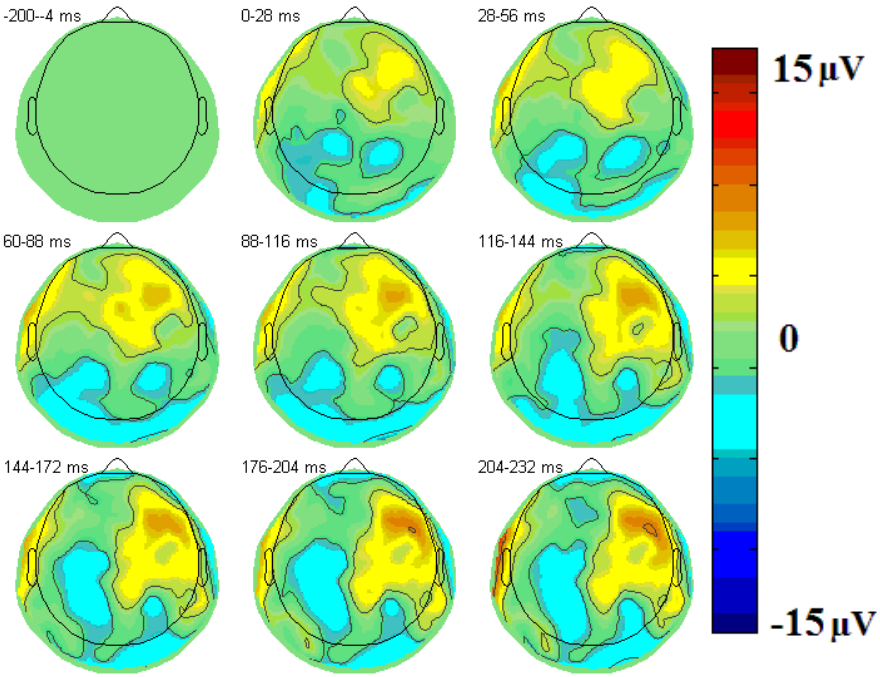


Figure J. 8. Topographical plots of the response to targets on the **right** side of the screen in **competition** conditions in infants between **2.5-3.5 months** of age.

3.5-5.5 months

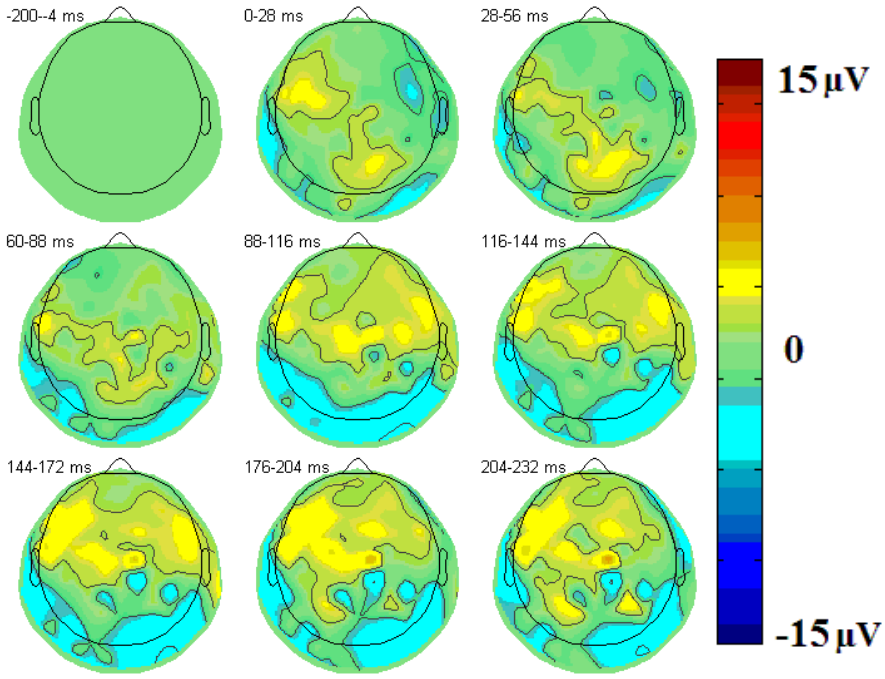


Figure J. 9. Topographical plots of the response to targets on the **left** side of the screen in **non-competition** conditions in infants between **3.5-5.5 months** of age.

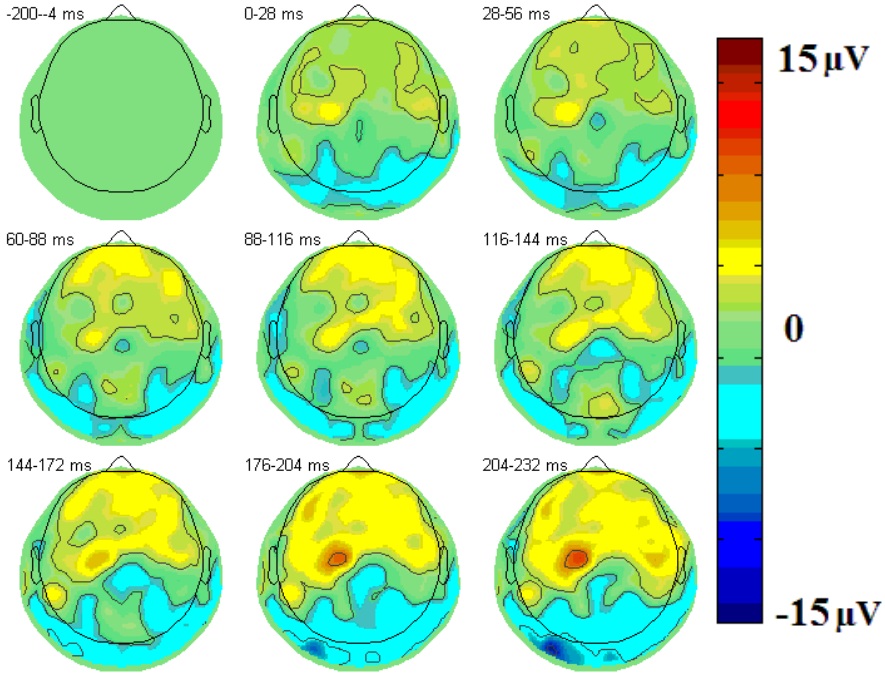


Figure J. 10. Topographical plots of the response to targets on the **right** side of the screen in **non-competition** conditions in infants between **3.5-5.5 months** of age.

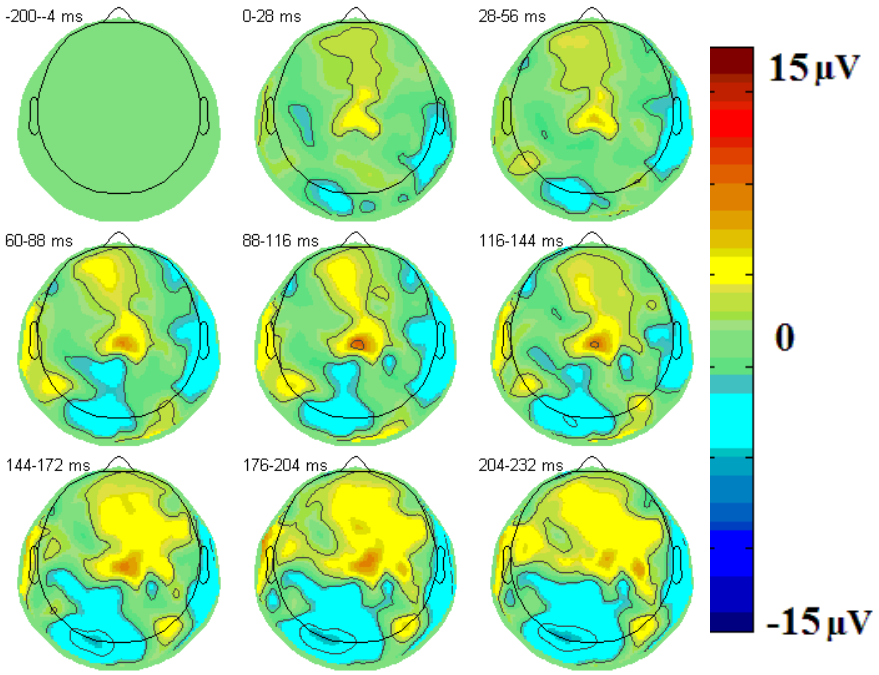


Figure J. 11. Topographical plots of the response to targets on the **left** side of the screen in **competition** conditions in infants between **3.5-5.5 months** of age.

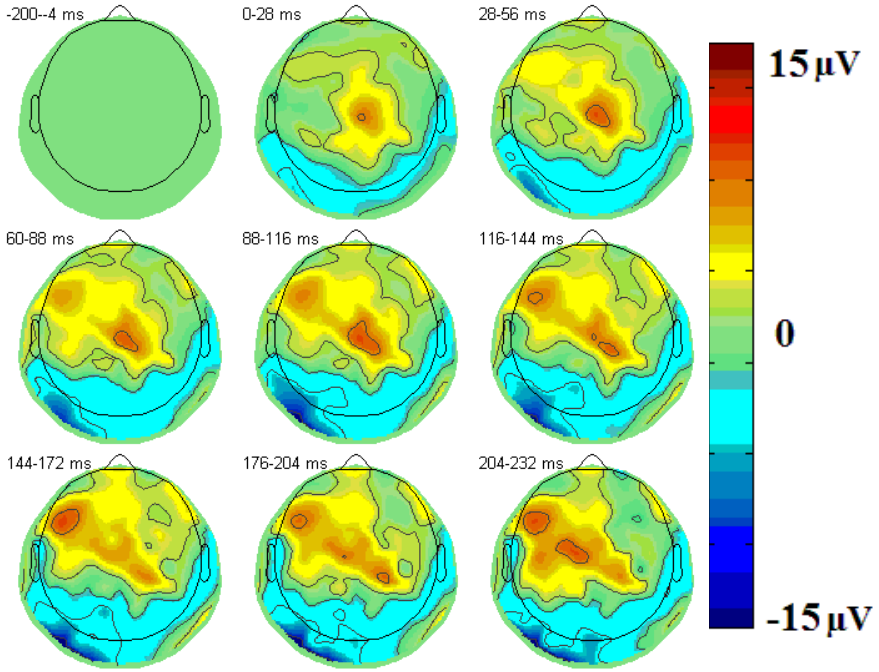


Figure J. 12. Topographical plots of the response to targets on the **right** side of the screen in **competition** conditions in infants between **3.5-5.5 months** of age.

5.5-7.5 months

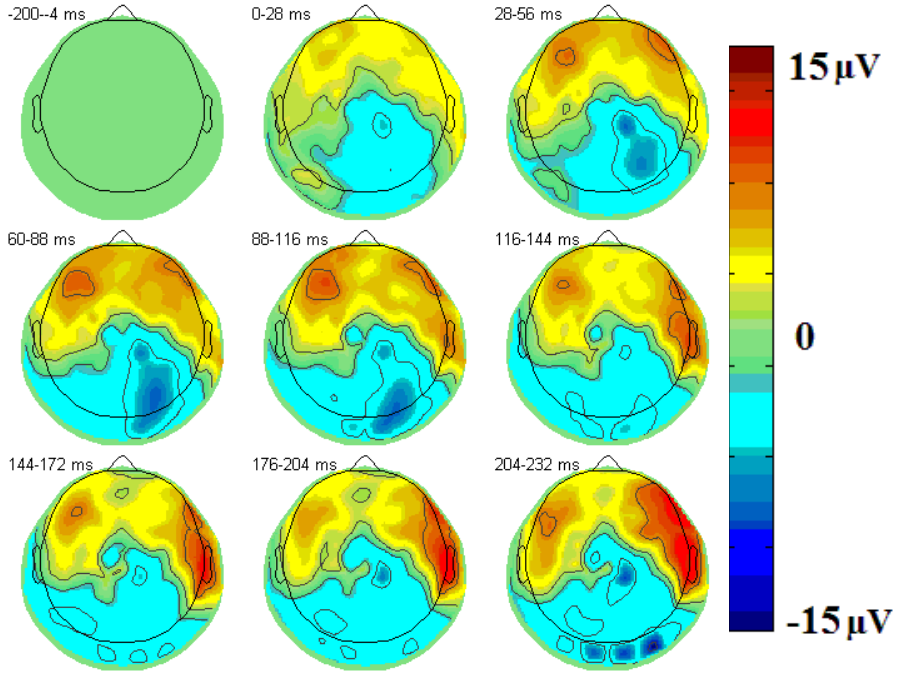


Figure J. 13. Topographical plots of the response to targets on the **left** side of the screen in **non-competition** conditions in infants between **5.5-7.5 months** of age.

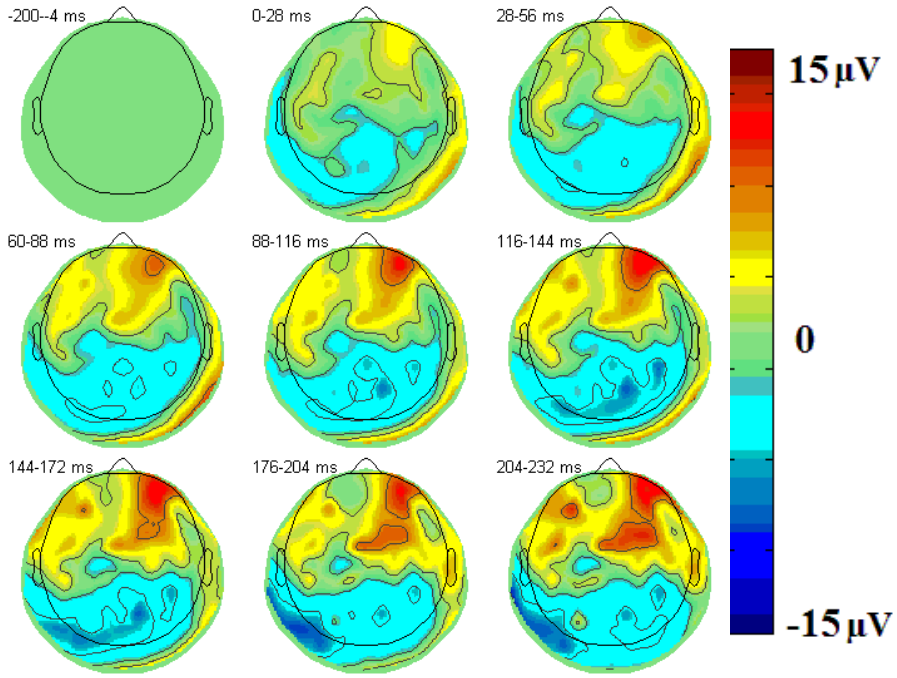


Figure J. 14. Topographical plots of the response to targets on the **right** side of the screen in **non-competition** conditions in infants between **5.5-7.5 months** of age.

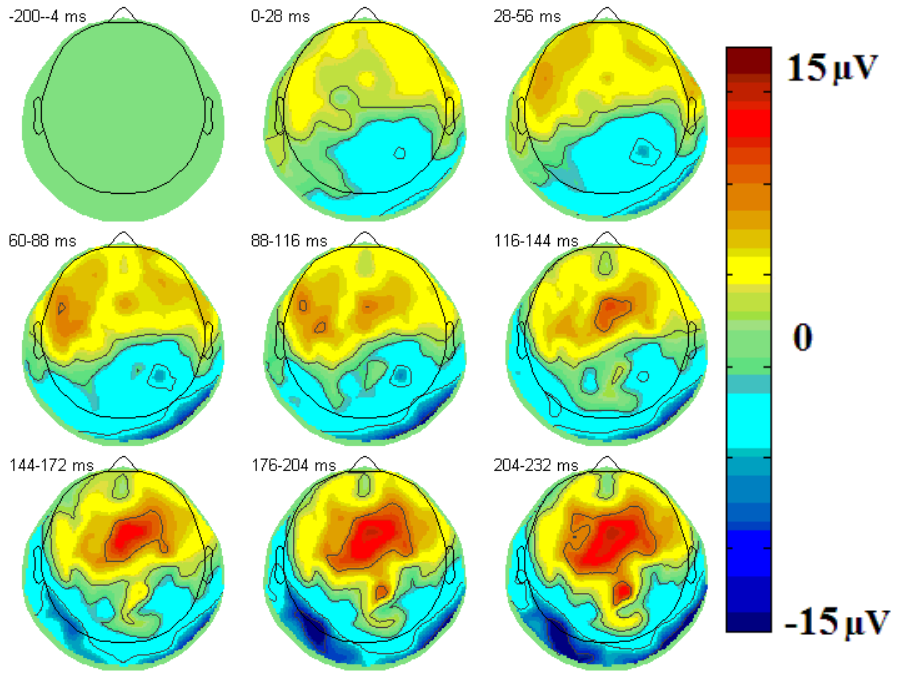


Figure J. 15. Topographical plots of the response to targets on the **left** side of the screen in **competition** conditions in infants between **5.5-7.5 months** of age.

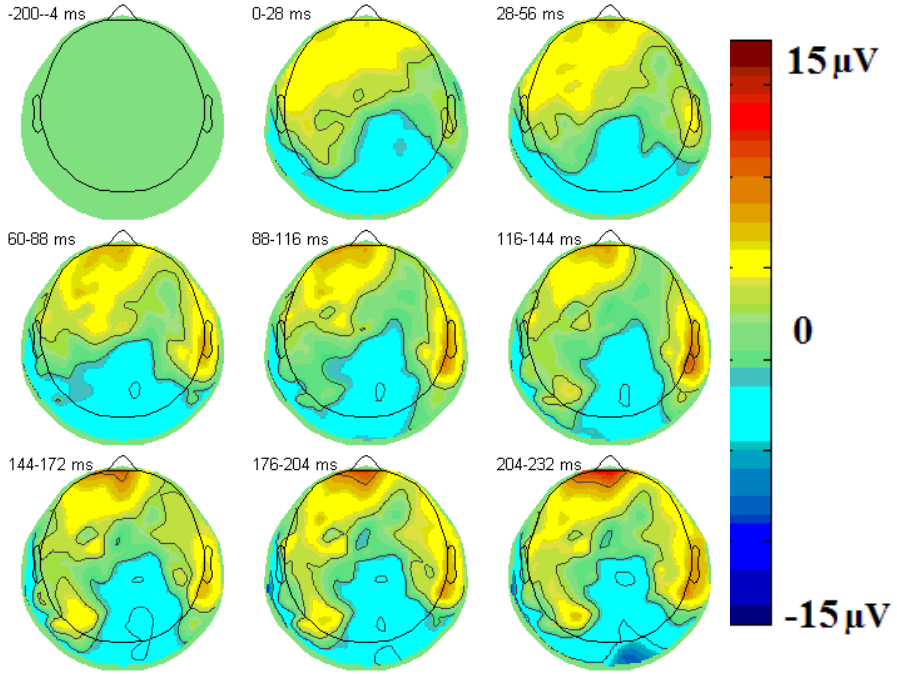


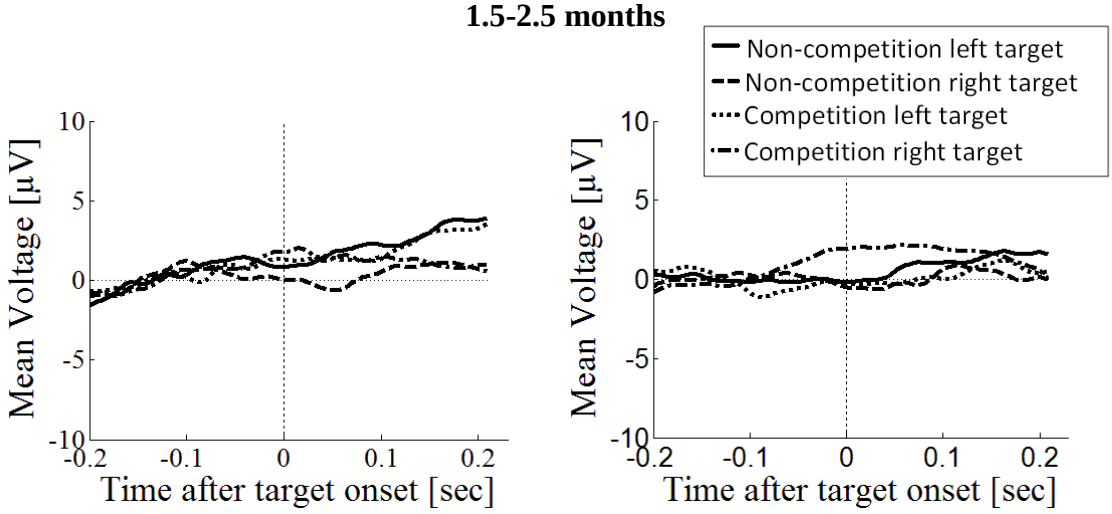
Figure J. 16. Topographical plots of the response to targets on the **right** side of the screen in **competition** conditions in infants between **5.5-7.5 months** of age.

Appendix K. Wave plots of infant responses (Chapter 6)

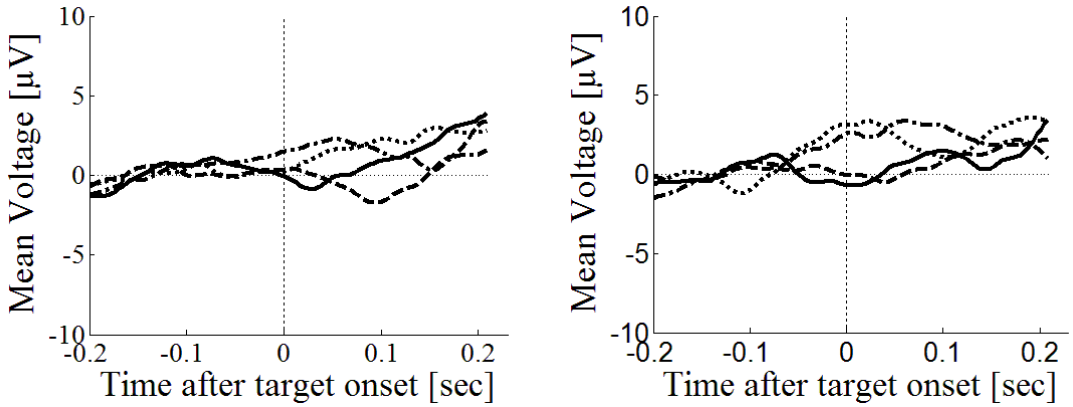
Frontal areas

Topographical plots show brain responses in fronto-central areas (see Chapter 2, Figure 2.5 for details on the electrode locations) in the left (left) and right (right) hemisphere, averaged across all infants who completed the minimum trial number of 5 trials per condition, as described in Chapter 6. Younger infants are displayed at the top, older infants at the bottom. The continuous line displays left non-competition (-), the dashed line right non-competition (--), the dotted line left competition (···) and the dash-dotted line right competition conditions (-·-).

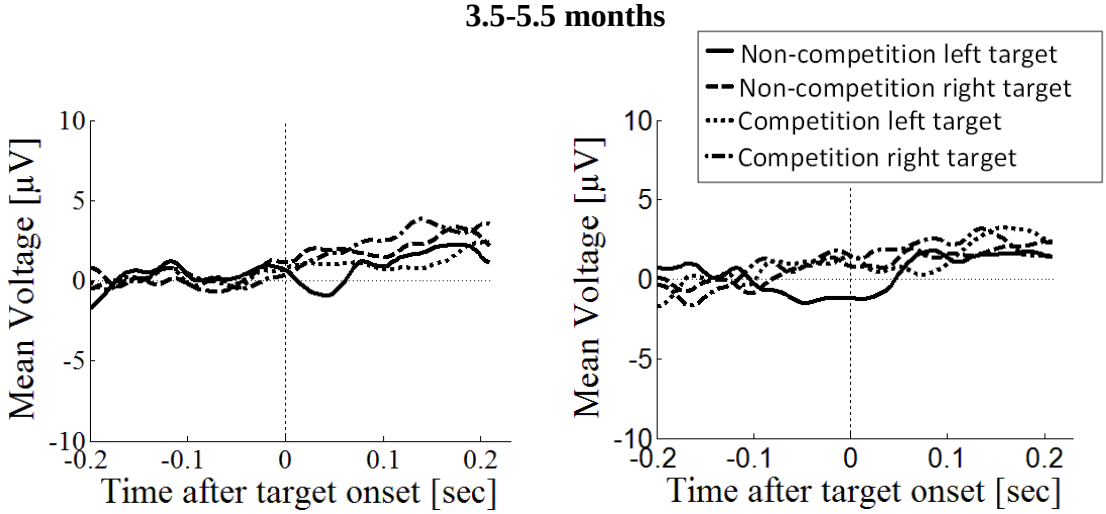
1.5-2.5 months



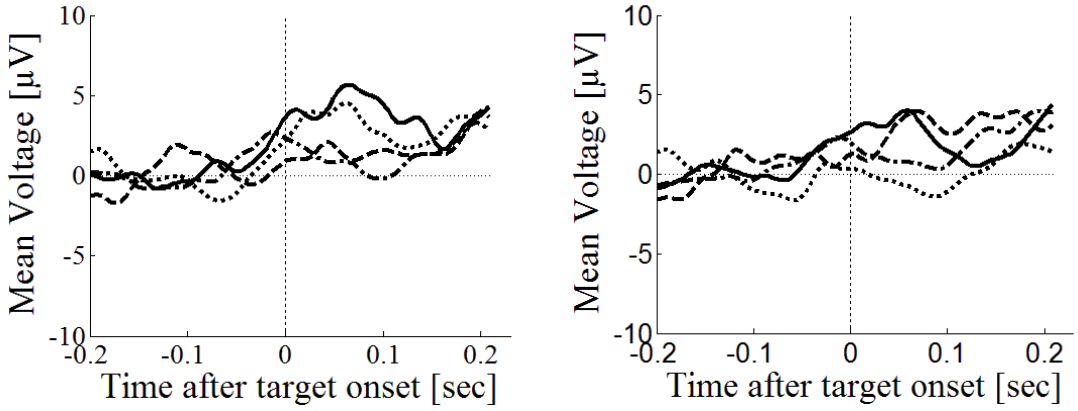
2.5-3.5 months



3.5-5.5 months

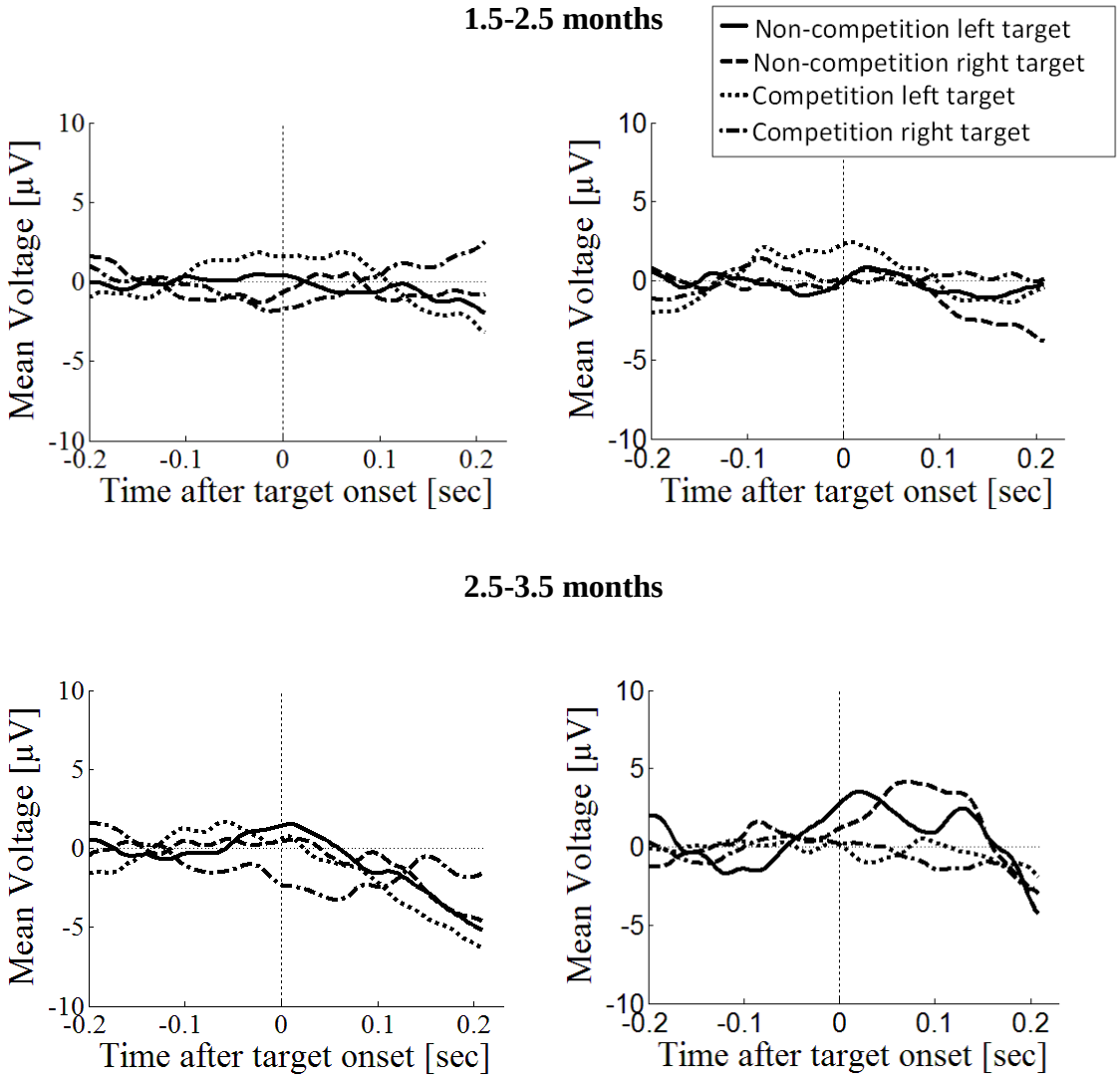


5.5 to 7.5 months

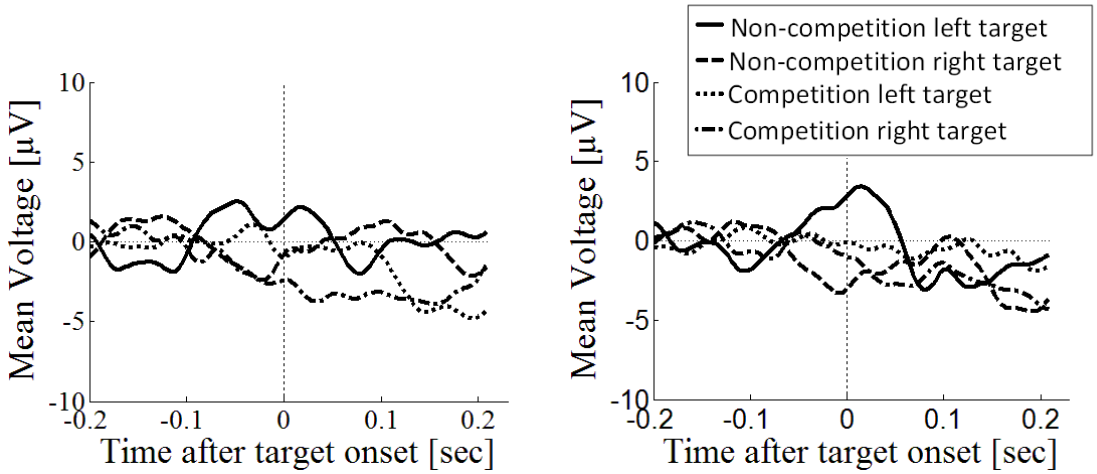


Occipital areas

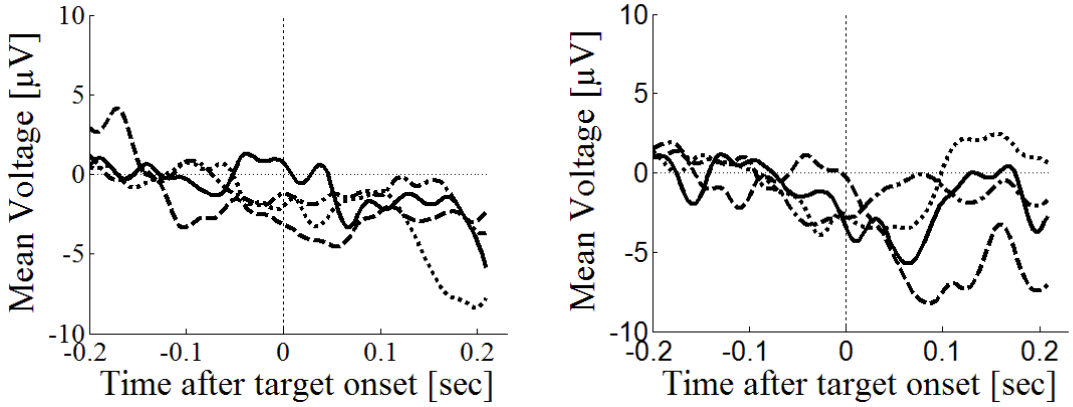
Topographical plots display brain responses in lateral occipital electrode clusters around electrodes O1 and O2 (see Chapter 2, Figure 2.4 for a visualisation of the electrode locations) for the left (left) and right (right) hemisphere. Younger infants are displayed at the top, older infants at the bottom. The continuous line displays left non-competition (-), the dashed line right non-competition (--), the dotted line left competition (···) and the dash-dotted line right competition conditions (-·-).



3.5-5.5 months



5.5-7.5 months



Appendix L. ERP analyses for all infants in Chapter 6

The ERP analysis described in Chapter 6, section 6.3.3 was repeated including all infants, including the ones who did not meet the strict minimum trial number criterion (> 5 trials per condition).

Frontal response

The mean amplitude in frontal areas was -2.40 µV (*SD* = 65.98 µV, *median* = 1.01 µV, 25th p*ercentile* = -3.96 µV, 75th *percentile* = 6.23 µV, *interquartile range* = 10.19 µV). After excluding outliers, a mixed model was computed, including participants as random effects and number of target (1 or 2), condition (non-competition vs competition), time window, age group and brain hemisphere (ipsi- vs contralateral) as fixed factors.

There was a marginal effect of number of targets, $F(1, 3266) = 3.76$, $p = .053$, $d = 0.495$, with greater amplitudes for single targets ($M = 1.32$, $SD = 5.85$) than for double targets ($M = 1.01$, $SD = 6.64$), an interaction of age group and condition, $F(3, 3273) = 5.36$, $p = .001$, and a three-way interaction of age group, condition and number of targets, $F(3, 3268) = 10.44$, $p < .001$.

Separate analyses were repeated for single and double target trials. In single target trials, there was a significant interaction effect of condition and age group on mean amplitude, $F(3, 1705) = 3.05$, $p = .028$, showing an increase in amplitude with age in the non-competition condition, while the amplitude did not change with age in the competition condition (Figure L.1). Double target trials showed an interaction of condition and age group, $F(3, 1530) = 9.77$, $p < .001$.

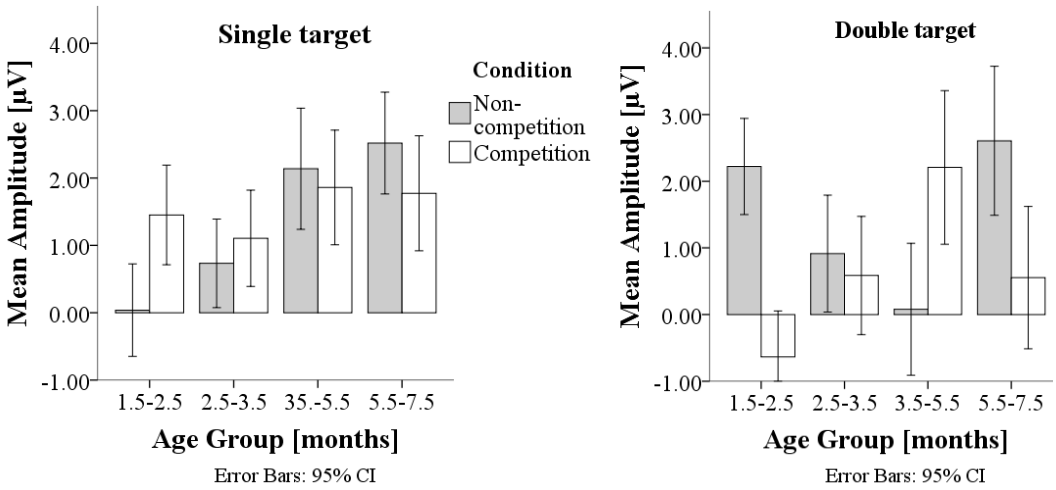


Figure L. 1. Overall amplitudes increase with age for single targets, particularly in the non-competition condition.

Posterior negativity

The mean amplitude in occipital areas was -0.33 µV (*SD* = 22.52 µV, *median* = -0.70 µV, 25^{th} *percentile* = -7.03 µV, 75^{th} *percentile* = 5.77 µV, *interquartile range* = 12.80 µV). After excluding outliers, a mixed model was computed, including participants as random effects and number of target (1 or 2), condition (non-competition vs competition), time window, age group and brain hemisphere (ipsi- vs contralateral) as fixed effects.

There was an interaction of condition and age group, $F(3, 3299) = 9.45$, $p < .001$. Separate analyses were conducted for single and double target conditions. Single target conditions showed an effect of time window, $F(3, 1733) = 2.66$, $p = .047$, with greatest amplitudes between 50 and 100 ms (Table L.1), and an interaction effect of condition and age group. $F(3, 1746) = 11.40$, $p < .001$ (Figure L.2). Double target conditions also showed a significant interaction effect of condition and age group, $F(3, 1518) = 2.68$, $p = .045$, Figure L.3.

Table L. 1. *Mean amplitudes (in µV) increase over time in single target conditions, while they decrease over time in double target conditions. In both single and double target conditions amplitudes are highest between 50 and 100 ms after target onset.*

Time window	Mean (SD) single	Mean (SD) double
0-50 ms	-0.41 (6.58)	-1.07 (7.68)
50-100 ms	-1.51 (7.58)	-1.33 (8.58)
100-150 ms	-1.38 (7.85)	-0.30 (8.98)
150-200 ms	-1.27 (8.05)	-0.20 (9.10)

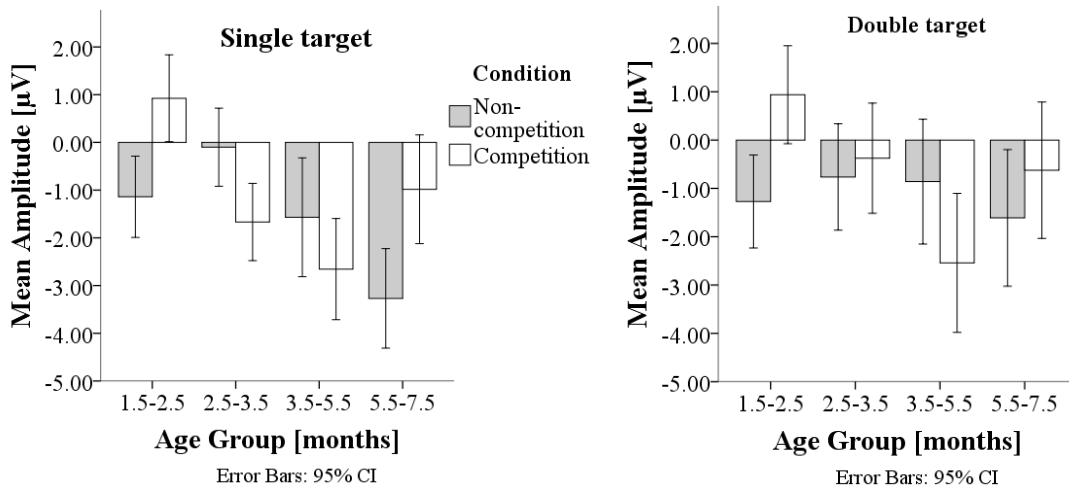


Figure L. 2. Amplitudes of the negativity in single target conditions (left) increase with age, especially in the non-competition condition. The interaction effect is less clearly visible in double target conditions (right).

Appendix M. Attention between 6 and 10 years: Preliminary results of a rapid test using touchscreen responses and relation to MRI measures

Supported by a Bogue Research Fellowship, I had the opportunity to visit the Center for Human Development of the University of California, San Diego to become involved in the Longitudinal Study of School Age Children (PLING) under supervision of Professor Terry Jernigan. In the frame of this large scale study directed by Professors Terry Jernigan and Anders Dale, I was able to collect data on attention development in a subset of the children tested for PLING for a pilot study, which will be presented in this section.

Background

Behavioural development

Several tasks allow a monitoring of attention development in childhood, most of which involve verbal instructions and understanding of the task (e.g. Test of Everyday Attention for Children, Manly et al., 2001) and often take a substantial time to complete. During infancy, the Fixation Shift Paradigm (Atkinson & Braddick, 2012; Atkinson et al., 1988; Braddick & Atkinson, 1988; Colombo, 2001; Hood & Atkinson, 1990, 1993; Matsuzawa & Shimojo, 1997) can be used to measure the ability to disengage and shift attention by monitoring saccades between stimuli. Similar measures to the Fixation Shift Paradigm are suitable in later childhood. Klein, Raschke, and Brandenbusch (2003) used the pro- and anti-saccade task, where children were instructed to look at a peripheral target in competition and gap conditions. They found a significant effect of condition (gap or competition) on saccade latencies (also found by: van der Geest, Kemner, Camfferman, Verbaten, & van Engeland, 2001), a decrease in saccade latency between 7 and 10 years of age and slower saccade latencies in Attention-Deficit Hyperactivity Disorder (ADHD) patients than in controls. This indicates that the ability to shift attention improves with age and that this feature is impaired in children with attention deficits. Similar effects could be found when measuring manual responses instead of saccade latencies, although the facilitation in the gap condition was smaller for manual than for saccadic responses (Iwasaki, 1990).

Brain development

Connections in the brain develop extensively during infancy and childhood (Burkhalter, 1993; Huttenlocher, 1979; Petanjek et al., 2011). Diffusion tensor magnetic resonance imaging (DTI) allows to investigate these connections in vivo (Basser, Mattiello, & LeBihan, 1994; Makris et al., 1997). The organisation and integrity of fibre tracts can be measured as fractional anisotropy (FA), which describes the diffusion of water molecules and how it differs in the direction along the tract from other directions (e.g. Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). The variation in FA between different individuals or between individuals of different ages can then be compared using Tract-Based Spatial Statistics (TBSS, Smith et al., 2006).

The superior longitudinal fascicle (SLF) is a major fibre tract that connects "frontal, occipital, parietal and temporal lobes" of the cerebrum (Merchant, 2011, p.2436). It has been shown to be involved in processes of visual attention, as it is impaired in patients with spatial neglect (e.g. Shinoura et al., 2009), and shows lower FA values in patients with ADHD (Hamilton et al., 2008; Konrad et al., 2010) especially in the right SLF (De Schotten et al., 2011). Furthermore, research demonstrates that the SLF significantly matures during childhood and adolescence (Lebel & Beaulieu, 2011; Lebel et al., 2008; Zhang et al., 2007), supporting the idea that impairments might develop in this period.

Aims and hypotheses

The aim of this study was to use the FSP as a quick, portable and simple attention measure to monitor changes in the ability to shift attention in competition and non-competition conditions during childhood and their relation to the development of cortical connectivity. Therefore, a touch screen version of the FSP was developed, including the double target condition which involves additional cognitive processing (Kulke et al., 2014a, 2014b) and might provide more fine-grained assessment of cognitive abilities. DTI was used to measure brain development and investigate basic changes in attention-related brain connectivity during early childhood. It was predicted that the ability to shift attention in the tablet version of the FSP improves with age and coincides with maturation of the SLF.

Method

Participants

Thirteen children between 6 and 10 years of age (M_{age} = 8.38, *SD* = 1.50) participated in the frame of "Data Camps" at the University of California, San Diego (UCSD), which were part of the PLING study, following up on the Pediatric Imaging, Neurocognition and Genetics (PING) study (Center for Human Development, 2011; Fjell et al., 2012). They were recruited from local public and charter schools, music and martial arts training programs, and community events such as science fairs and music and athletic exhibitions. Parents consented to their participation in research, verbal and written assent was granted by the children before participation and they were informed that they could stop the testing at any time. Children received a colourful eraser in return for their participation. Participants were paid $50 per MRI session. Ethics for the project were approved by the UC San Diego Human Research Protections Program.

Materials and Stimuli

Stimuli were designed on the basis of Hood and Atkinson (1993), as described by Kulke et al. (2014a, 2014b). The stimulus presentation programme was written in Python. Stimuli were generated by a Lenovo touch screen laptop (Lenovo Yoga 2 Pro Multimode Ultrabook with full windows touch support) in a Windows 8.1 (2013 Microsoft Corporation) 64-bit operating system (8GB RAM), using PsychoPy (version 1.80.06, 2002-2014, Jonathan Peirce) as presentation programme and presented on a 13.3'' (33.8 cm, 3200x1800 pixel) QHD + LED touchscreen with a sampling rate of 48 Hz. Stimuli appeared on a grey background. Each trial started with the first stimulus, a black schematic face that changed "expression" at a rate of 3 reversals per second, being presented in the centre of the screen. Children were seated comfortably in front of the computer at an approximate distance of 40 cm from the screen. At this distance, the face subtended a visual angle of 7.2° x 7.2° (4.5 x 5 cm). After a random inter-trial interval (ITI) between 0.5 and 2.5 seconds the second stimulus (target) appeared, a grating made of one black and one white rectangle that reversed colour 3 times per second and appeared in the left or right visual field (single target condition) or on both sides of the visual field (double target condition) at an eccentricity of 14.5° (10.2 cm). It subtended a visual angle of 4.6°x19.3° (13.6 x 3.2 cm). In the non-competition condition, the central face disappeared when the peripheral target appeared, while in the competition condition it remained present throughout the trial (Figure M.1). Subjects were instructed

to touch the bars as quickly as possible. They heard a positive brief high beep after every correct response and a long low beep after an incorrect response. After completing the task children saw a rewarding colourful screen with jungle animals and heard a children's song.

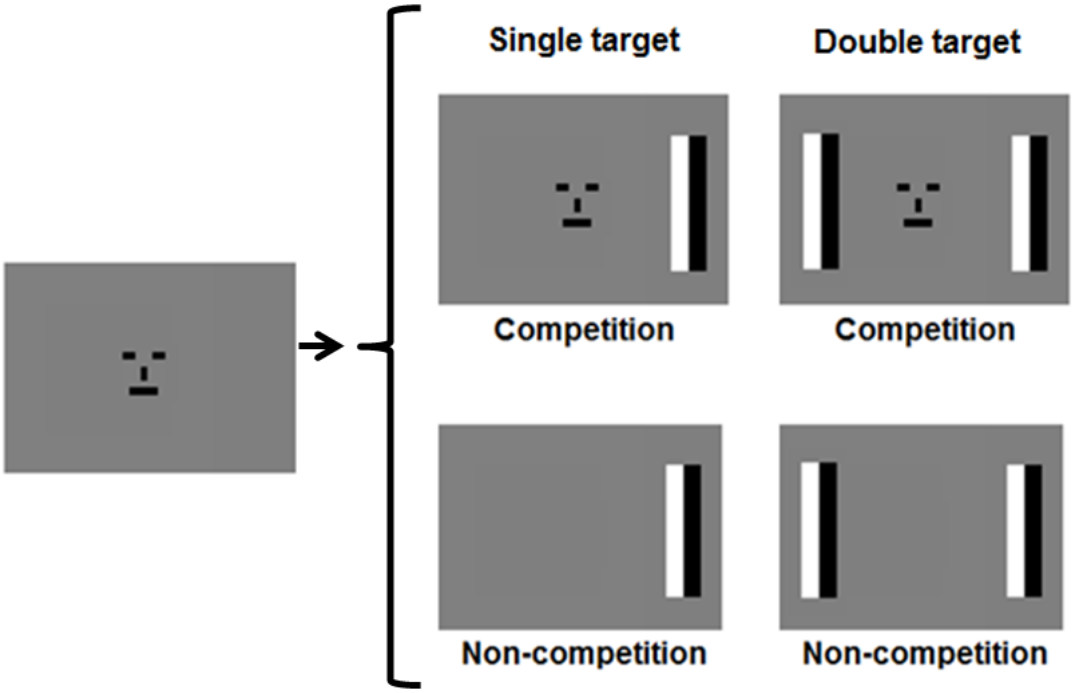


Figure M. 1. Order of displays shown in competition and non-competition conditions containing single or double targets.

Design

A mixed design measured the effect of the within-subject factors condition (competition or non-competition) and number of targets (one or two targets) and the between-subject factors age group (6, 7, 8, 9, 10 years) on the ability to switch attention, operationalized as the latency of a manual reaction (touch) towards the target. Fractional anisotropy of the superior longitudinal fasciculus was correlated with reaction time measures.

Procedure

For the behavioural task, the child was seated comfortably in front of the tablet. To make the task more engaging, children were told that a hunter (central face) wants to catch zebras (peripheral bars) and they were instructed to warn the zebras by touching the peripheral bars as quickly as possible. Children completed 6 practice trials (one per condition) before the start of the experiment and they were encouraged to ask questions.

During the main experiment, conditions were presented in a pseudo-random order and the side on which the target appeared was selected pseudo-randomly. The children completed 60 trials, which took them approximately 3-5 minutes.

MRI

The MRI scanning (for the full protocal see: Fjell et al., 2012) took place in the UCSD Multimodal Imaging Lab (MMIL). Children and parents were asked about metal in the child's body and children were scanned for metal using a metal detector. To get familiar with the scanning process, children had the opportunity to visit a mock scanner, an old scanner model that imitated sounds and process of normal scanning and familiarized them with the procedure. Images were acquired on a Siemens 3 tesla scanner. Data acquisition took approximately 1 hour, including 3-D T1-weighted scans, a T2-weighted volume, a set of diffusion-weighted scans with multiple b values and diffusion reactions, scans to estimate MRI relaxation rates and optional gradient echo-planar imaging scans for resting state functional MRI. Adaptive motion compensation, using "PROMO", a real-time motion correction algorithm, was used during scanning to reduce motion artefacts. Children watched movies during the majority of the scan. Data processing was completed with Freesurfer, TBSS tools in FSL and an atlas-based method for labelling and characterizing fiber tracts developed in the MMIL.

Results

To eliminate outliers, RT values under 0.15 sec were excluded from further analyses, as they are unlikely to be caused by the appearance of the stimulus. Values that deviated more than 3 SD from the mean reaction time (M = 0.724 sec, SD = 0.475 sec) were excluded, as they might partially be related to distraction of the child. Analyses were performed in SPSS (version 20, IBM Statistics).

A linear mixed effects model including subject effects as random effects showed a significant decrease in reaction times with age, $F(4, 8.515) = 6.70$, $p = .010$, Figure M.2. The condition and number of bars did not have a significant effect on RTs and they did not interact with the effect of age (Table M.1), despite a tendency for children to be slower when reacting to two bars (Figure M.3). Adding the factor gender to the model did not reveal a significant effect, $F(1, 4.615) = 1.20$, $p = .327$, so it was excluded from further analyses.

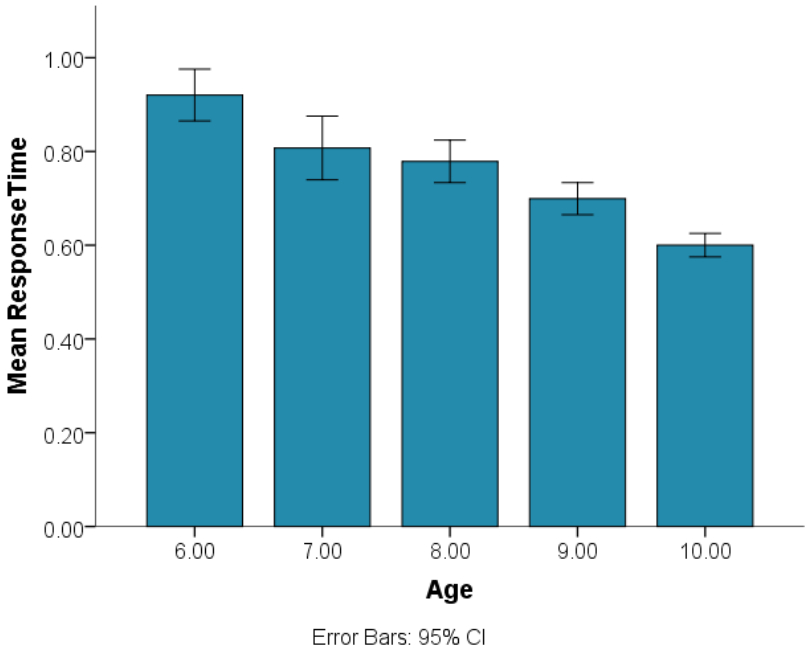


Figure M. 2. The mean response time significantly decreases with age.

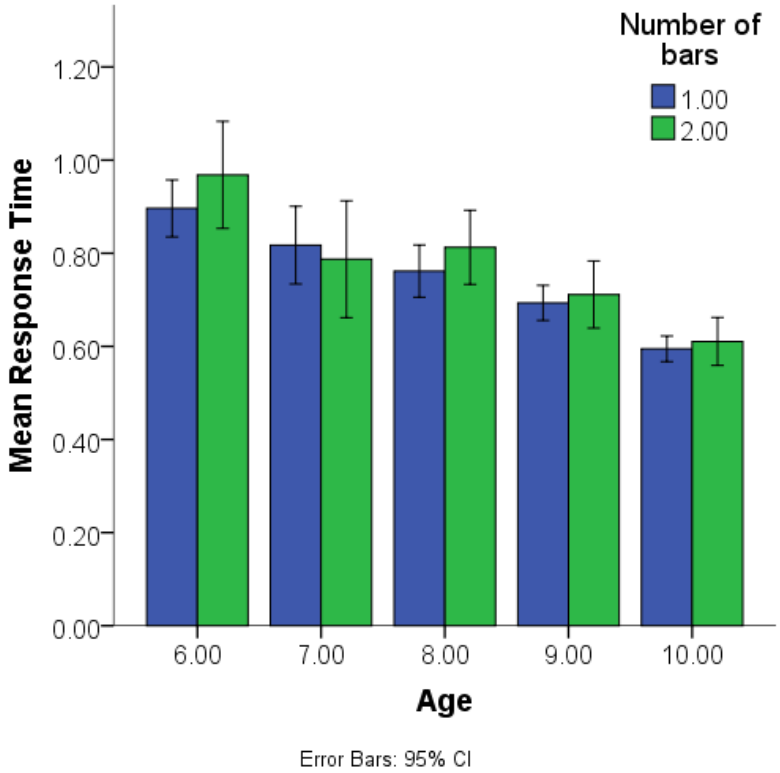


Figure M. 3. Reaction times over age split on whether one or two bars were presented. Children take slightly longer to react if two bars are present than if only one bar was visible.

Table M. 1. *F-values and p-values for the effects that were observed.*

Effect source	F-value	p-value
Condition (competition vs non-competition)	0.17	. 684
Number of target stimuli (1 vs 2)	1.50	.221
Age	6.70	.010*
Age * Condition	1.01	.401
Age * Number of bars	0.60	.660
Age * Condition * Number of bars	0.11	.978

A further analysis was performed that included outliers, as they can indicate lapses of sustained attention, distractibility or sticky fixation. Trials with reactions that were quicker than 0.15 seconds after target onset were excluded as they are unlikely to be related to the appearance of the target. The same pattern of results as before was replicated, showing a significant effect of age on response times, $F(4, 720) = 20.24$, $p < .001$, a tendency for children to react slower when two stimuli were present than when only one stimulus was present, although this tendency was not significant, $F(1, 720) = 3.24$, $p = .072$, and no effect of competition conditions (Table M.2)

Table M. 2. *F-values and p-values for the effects that were observed when outliers were included in the analysis.*

Effect source	F-value	p-value
Condition (competition vs non-competition)	0.03	.871
Number of target stimuli (1 vs 2)	3.24	.072
Age	20.24	<.001***
Age * Condition	0.49	.741
Age * Number of bars	1.12	.348
Age * Condition * Number of bars	0.51	.729

For a sample of this size it would not be possible to expect conclusive results on brain-behaviour correlation, therefore an investigation of relationships between behavioural response latencies and DTI measures was conducted on an exploratory basis. Differences in fractional anisotropy in the right SLF were investigated. A linear model showed a small non-significant effect of age on fractional anisotropy, $F(1, 12) =$

3.42, p = .089, suggesting increasing FA values with age. Correlations between reaction times and DTI values were computed. The latency difference between competition and non-competition conditions showed a negative correlation which approached significance with fractional anisotropy in the right SLF, r = -.397, p = .083. There were no further correlations between DTI values and behavioural response latencies in any of the separate conditions.

Discussion

Reaction times towards peripheral stimuli decreased with age, but no effect of competition, number of targets or gender was found. This confirms that only the general ability to shift attention improves between 6 and 10 years of age and that this improvement can be measured using portable touchscreen computers.

As the task is short (<3 minutes), it can be used as a quick test for attention development. As previous literature found general differences in latencies between ADHD patients and controls (Klein et al., 2003), it might be possible to develop this task to be a quick test for abnormalities in attention development.

As the current data set is pilot data gathered through a feasibility study, the lack of a significant effect of condition may be due to the small sample size of only 13 children combined with the presence of age variation in the sample. Furthermore, additional reaction time noise is introduced through the response mode (manual response instead of saccadic response), as Iwasaki (1990) showed that the competition effect is smaller for manual responses than for saccadic responses. Effects might further be reduced as a result of the temporal inaccuracy of the method, as the touchscreen has a less consistent sampling rate (up to 48 Hz, but varying) than eye-tracking (~60Hz). In order to keep this method simple and portable, while improving temporal accuracy and power, it would be possible to combine it with the cheap and portable eye-tracker (e.g. Tobii EyeX, £55) to investigate potential effects of condition on saccade latency.

There is also a possibility that by age 6 years children have fully automated their responses and take no extra time to disengage from the central target under competition. As previous research shows that competition effects can still be found in adult subjects when using more exact measures (Kulke et al., 2014a, 2014b), it is more likely that the lower sampling rate of the touch screen resulted in the differences being covered up or that the small sample size led to insufficient power to detect these effects. In order to further investigate the possibility that competition effects are abolished in children, it would be necessary to test children younger than 6 years.

Neuroimaging measures show that fractional anisotropy marginally increases with age and marginally correlates with the difference in behavioural performance between the competition and non-competition conditions. The lower the difference in reaction times between competition and non-competition conditions was (i.e. the more efficiently children could disengage attention), the higher the FA values in SLF. This relationship between attention performance and SLF is in line with previous literature showing lower FA values in patients with attention impairments (Hamilton et al., 2008; Konrad et al., 2010; Shinoura et al., 2009) especially in the right SLF (De Schotten et al., 2011). This suggests that the SLF may play a crucial role for disengagement of attention. As only a small number of subjects were tested for this study, neural results need to be replicated with a greater sample size to make any inference from this.

In conclusion, this pilot study suggests that the short and engaging task used here may be valuable for mapping changes in the ability to shift attention with age and correlate them with neural measures. Further research is required to replicate findings to infer to a wider population.

Acknowledgements

Thanks go to Prof Terry Jernigan who supervised my research visit to UCSD and to the friendly team of researchers at the Center for Human Development who made this pilot study possible by helping me with numerous aspects of testing and recruitment and who made my research visit a very enjoyable stay. I would particularly like to mention Melanie Maddox, Sarah Archibald, Janet Shin and Ingrid Piper. Special thanks go to Nolan O'Dowd for his programming support and to Dr Erik Newman for his advice on MRI. This research was made possible through a Bogue Fellowship.

Appendix N. A pilot study showing atypical attention development in very mildly preterm-born infants

The ability to shift attention does not always develop normally, but impairments can be found in different developmental disorders. The Fixation Shift Paradigm (FSP) detects impairments at an early age (Atkinson & Braddick, 2007; review: Atkinson & Braddick, 2011; review: Atkinson & Braddick, 2012; Atkinson et al., 2008; Mercuri et al., 1997; Mercuri et al., 1998) and can be used to predict future cognitive development (Atkinson et al., 2008; Mercuri et al., 1999). In particular, very premature infants show impairments in the ability to shift attention under competition (Atkinson & Braddick, 2007; Atkinson et al., 2008). In scientific studies of food supplements, the FSP has been used as a surrogate outcome measure with preterm infants (Atkinson et al., 2014). Late and moderately preterm born infants have a risk of cognitive impairment later in life (e.g. S. Johnson et al., 2015). Problems related to premature birth have been suggested to be treatable with food supplements that add deficient nutrients to the patient's diet (Koletzko et al., 1989; Lucas et al., 1998). As nutritional supplements can be given from early age on, the treatment outcome could profit from early detection of delayed development and the validity of the treatment effect can be investigated using the FSP. Therefore, the FSP provides a basis for intervention development that can help to give at-risk infants a chance to lead a normal life.

On contrary, one study on healthy, low-risk premature infants showed that they were better at disengaging attention than their term-born peers (Hunnius et al., 2008). Hunnius et al. (2008) propose that developmental advantages in preterm infants may be related to an earlier exposure to visual input. Generally, difference between term-born and premature infants can be found from an early age on and they have a diagnostic value for early detection of developmental delays.

In previous studies, trained adult observers judged saccade latencies on line, or time-consuming video-coding was used to determine saccade latencies. Particularly in a clinical context, the use of an automated eye-tracking approach for diagnostic purposes can save time (instead of video coding) and facilitate judgement (as the user does not need to be trained in observation techniques). Chapter 3 developed automated software that can be used to test infants' ability to shift attention in a quick and automated manner. This study aimed at testing this method on a group of mildly preterm-born infants to explore the diagnostic value of the automated approach. The aim was to

investigate whether differences between term-born and mildly premature infants could still be detected when eye tracking was used to judge saccade latencies instead of adult observers. This automated approach could then be used in combination with EEG to further explore which different neurodevelopmental mechanisms coincide with impaired attention development in preterm infants.

Method

Design

In a mixed design the effect of the within-subject factors condition (competition or non-competition), screen side watched (left or right) and the number of peripheral targets (one or two) and the between-subjects factors age group (< 4 months vs > 4 months) and prematurity (term-born vs mildly premature) on the dependent variables saccade latency and proportion of sticky fixations was measured. Due to the smaller number of premature subjects, infants were only split into two instead of previously four age groups.

Participants

Seventy-one healthy term-born infants (*Mean age* = 4.00 months, *SD* = 2.01, 38 female) born within 2 weeks of gestation who were recruited for the experiment in Chapter 6 were split into 2 groups: under 4 months (*n* = 43, *mean age* = 2.56 month, *SD* = 0.63) and over 4 months (*n* = 29, *mean age* = 6.14 months, *SD* = 1.35) and compared to 7 mildly preterm infants who were normal on neonatal neurological examination (see Table N.1 for chronological and gestational age). All participants were recruited from the Visual Development Unit's database and parents volunteered to participate with their infants in return for reimbursement of travel expenses to the Visual Development Unit. The study was approved by the UCL research ethics committee (Ref. number: 2002/02) and by the NHS (REC Ref. 14/LO/0610).

Table N. 1. *Ages, days born preterm and gestational ages of mildly preterm infants.*

Age [months]	Days preterm	Gestational age [weeks]
1.78	16	37.7
2.7	17	37.6
1.58	19	37.3
1.19	20	37.1
3.13	20	37.1
4.02	26	36.3
6.92	29	35.9

Materials, stimuli and procedure

Infants completed the same task as described in Chapter 6 for term-born infants under identical circumstances (see Chapter 6, section 6.2 for detailed descriptions). Before the participants arrived, the eye-tracker was calibrated on an adult using a standard five point routine to ensure a proper completion of the calibration (see Chapter 2, section 2.2.2 for details). Each trial began with a cartoon being presented on the computer screen to attract the infant's attention. If the experimenter judged the infant as alert, a black schematic face appeared. When the subject fixated on the face after a random inter-trial interval, target bars were randomly presented on the left, right or on both sides of the screen (see Chapter 6, Figure 6.1). In competition conditions the central face remained on the screen whereas in the non-competition condition, it disappeared at the onset of the bars. All conditions (number of bars and screen side and competition vs. non-competition) were presented in a random order.

Results

Data processing

The methodology chapter describes the method used for pre-processing eye-tracking and EEG data used throughout this thesis (see Chapter 2, section 2.2). Mixed linear models were calculated in SPSS (IBM Corp, 2011) and mixed effect logistic regressions were calculated in RStudio, Version 0.97.551, (Core Team, 2012). Prematurity was added as a categorical factor in the analyses.

Behavioural results

Infants who were born more than 14 days early were compared with term-born infants, using a mixed effects regression including participants as random effects and screen side, age group, condition, number of stimuli and prematurity code as fixed factors. In the following, saccade latencies are reported in ms.

Saccade latencies

Saccade latencies showed a significant effect of condition, $F(1, 3256) = 176.14$, $p < .001$, $d = 0.487$, with shorter latencies in the non-competition ($M = 560$, $SD = 499$) than in the competition condition ($M = 916$, $SD = 906$). Furthermore, there was a significant effect of prematurity, $F(1, 71) = 14.44$, $p < .001$, $d = 0.376$, with shorter latencies for term-born ($M = 701$, $SD = 703$) than preterm infants ($M = 1037$, $SD = 1050$). There was a significant interaction effect of age group and condition, $F(1, 3276) = 7.68$, $p = .006$, showing decreasing latencies in the competition condition with age; another significant interaction of condition and prematurity, $F(1, 3276) = 41.63$, $p < .001$, with greater differences between conditions in preterm than in term-born infants. Furthermore, there was a three way interaction of screen side, age group and prematurity, $F(1, 3323) = 4.65$, $p = .031$, showing that preterm infants were slower at shifting towards the left screen side in the older age group. A three-way interaction of age group, condition and prematurity, $F(1, 3276) = 49.33$, $p < .001$, showed that latencies under competition decreased with age in term-born but not in premature infants. Finally, there was a four way interaction of screen side, age group, condition and prematurity, $F(1, 3270) = 4.81$, $p = .028$.

Single target conditions

For single target conditions mixed effects regressions were computed including participants as random effects and age group, prematurity and condition as fixed factors. There was an effect of prematurity, $F(1, 69) = 12.40$, $p < .001$, $d = 0.391$, with shorter latencies for term-born infants ($M = 672$, $SD = 690$) than for premature infants ($M = 1011$, $SD = 1013$), and a significant effect of condition, $F(1, 2125) = 103.99$, $p < .001$, $d = 0.466$, with shorter latencies in the non-competition condition ($M = 539$, $SD = 491$) than in competition conditions ($M = 872$, $SD = 883$). There were interaction effects of age group and condition, $F(1, 2125) = 5.31$, $p = .021$, showing a greater latency decrease with age in competition than in non-competition conditions (Figure N.1). An interaction of prematurity and condition, $F(1, 2124) = 22.79$, $p < .001$, indicated a

greater disadvantage under competition for preterm than for term-born infants (Figure N.2). An interaction of age group, prematurity and condition, $F(1, 2124) = 30.57$, $p < .001$, showed that saccade latencies under competition decreased with age in term-born but not in preterm infants (Figure N.3).

In summary, saccade latencies were longer in competition than in non-competition conditions and this effect was greater for premature infants. Latencies decreased with age in term-born but not in preterm-born infants.

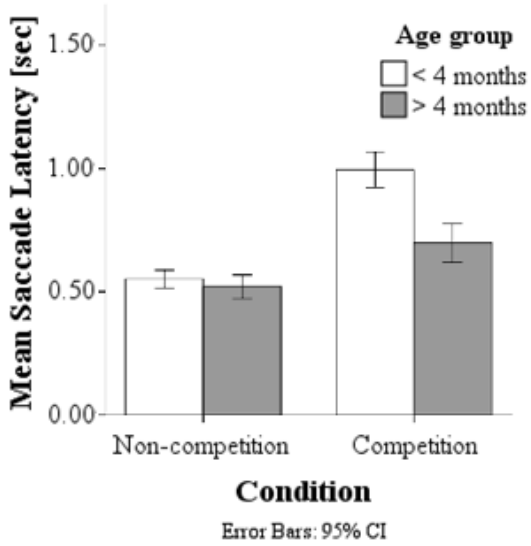


Figure N. 1. Saccade latencies towards single targets are shorter in non-competition than in competition conditions and this difference decreases with age.

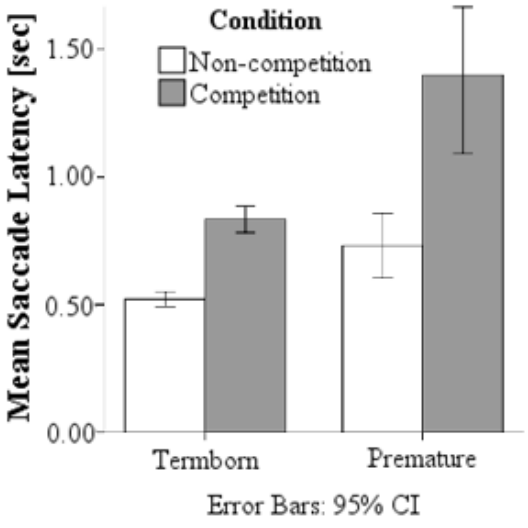


Figure N. 2. Saccade latencies towards single targets are shorter in non-competition conditions and shorter for term-born infants.

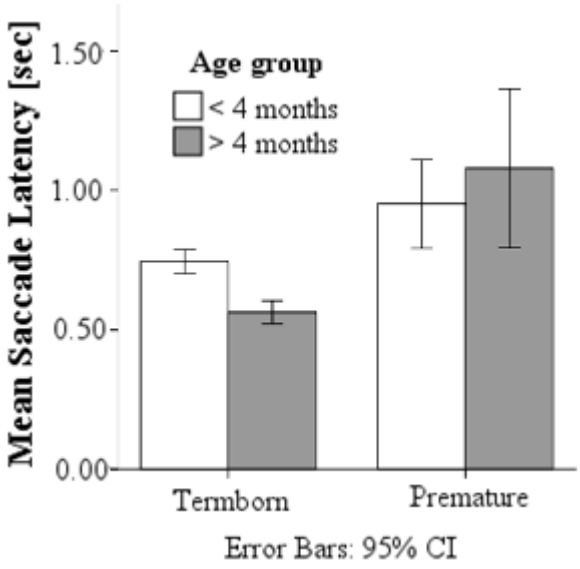


Figure N. 3. Saccade latencies towards single targets are shorter for term-born infants. Term-born infants become faster with age, while there is no difference between age groups for premature infants.

Sticky fixations

Mixed logistic regressions were computed to predict sticky fixations from the factors condition, age group, number of stimuli and prematurity.

There was a significant main effect of condition, $z = 5.48$, $p < .001$, with less sticky fixations in non-competition (1.1%) than in competition conditions (5.9%). A main effect of age group, $z = -2.73$, $p = .006$, showed more sticky fixations in younger (4.8%) than in older infants (1.6%). An interaction of condition and age, $z = -2.59$, $p = .010$, indicated decreasing proportions of sticky fixations with age (Figure N.4), and an interaction of condition and prematurity, $z = 2.23$, $p = .026$, indicated that premature infants show more sticky fixations in competition but not in non-competition conditions (Figure N.5).

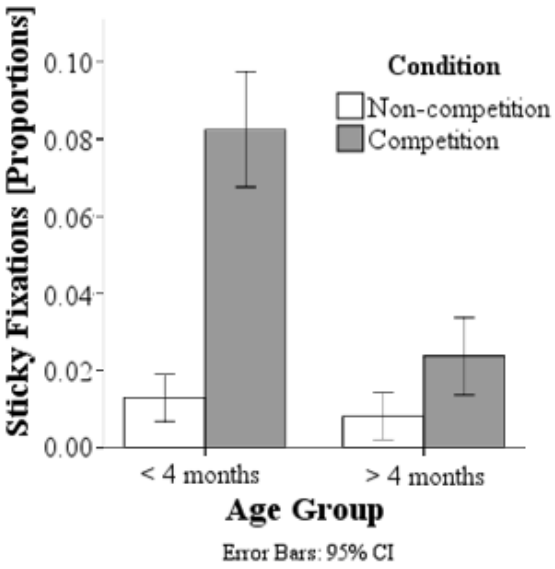


Figure N. 4. The proportion of sticky fixations decreases with age, particularly in the competition condition.

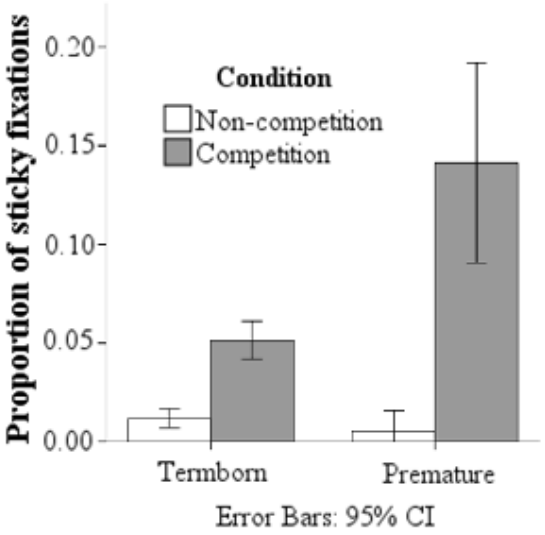


Figure N. 5. The proportion of sticky fixations is greater in competition than in non-competition conditions and the difference between conditions is greater for premature than for term-born infants.

Single targets

Single targets showed a significant main effect of condition, $z = 1.75$, $p < .001$, with less sticky fixations in non-competition (1.0%) than in competition conditions (6.3%), and an effect of age group, $z = -1.03$, $p = .043$, with more sticky fixations in young (4.9%) than in older infants (1.9%). Furthermore, there was an interaction of condition and age, $z = -1.73$, $p = .022$, showing a decrease in sticky fixations under

competition with age (Figure N.6), and a marginal interaction of condition and prematurity, $z = 2.20$, $p = .065$, showing more sticky fixations under competition in preterm than in term-born infants (Figure N.7).

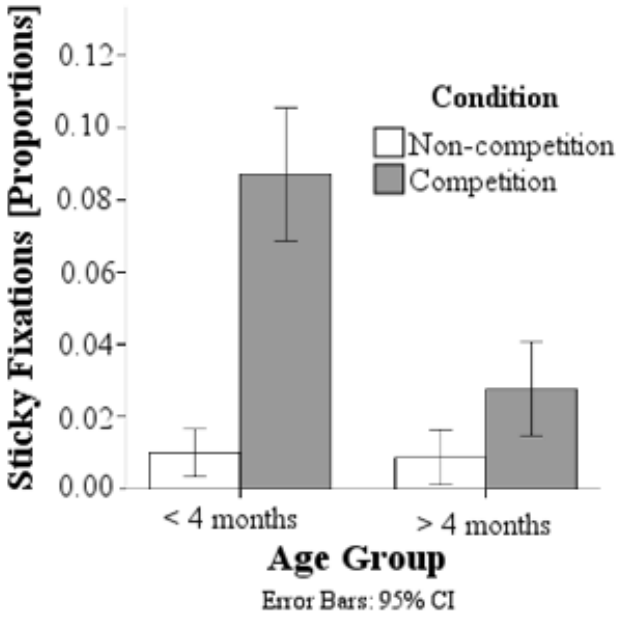


Figure N. 6. The proportion of sticky fixations in the single target condition decreases with age in the competition but not in the non-competition condition.

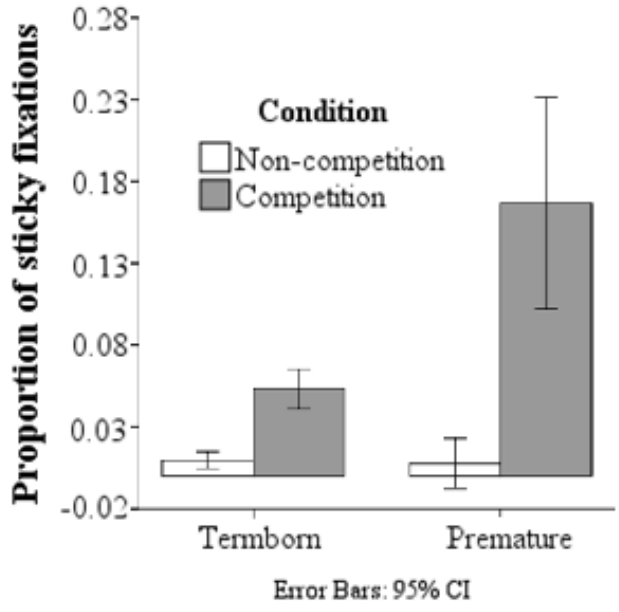


Figure N. 7. More sticky fixations occur under competition, particularly in premature infants.

Discussion

The aim of this study was to investigate whether differences in the ability to shift attention under competition between term-born and mildly premature infants could be detected when combining the FSP with eye tracking. It was hypothesized that findings using eye-tracking would be similar to previous findings with manual coding by adult observers. Results show significant differences between term-born and mildly premature infants, confirming the hypothesis and suggesting that eye-tracking is a valid tool to automate the FSP.

In line with previous research on premature infants, the mildly premature infants tested in this study showed impairments in shifting attention under competition compared to their term-born peers, measured by longer saccadic latencies and higher numbers of sticky fixations under competition. Furthermore, the mildly premature infants did not improve under competition with age, which is the pattern typically observed in term-born infants (Hood, 1995; Hood & Atkinson, 1993). This finding may reflect an overall impairment of saccadic shifts under competition. Alternatively, the development may be delayed; therefore, it would be interesting to test older age groups of preterm infants as well.

The findings in the current study contradict findings of Hunnius et al. (2008) who found healthy preterm infants to have a superior ability to shift attention compared to term-born peers. Their study differed from the current study in several aspects. Hunnius et al. (2008) used video recordings of talking or scrambled faces as stimuli, compared to colour reversing stimuli used in the current study. Furthermore, their stimuli were presented at a greater eccentricity (20° compared to 12.9° in this study). Appendix B showed that stimulus eccentricity had no significant effects on saccade latencies; however, the additional motion in video recordings may have influenced the effects found by Hunnius et al. (2008). Differences between their findings and findings from more severely impaired preterm infants (Atkinson et al., 2008) and the infants in the current study may be affected by moderating variables including the overall health of the infant, their state during testing, maternal age and stimuli and procedural differences. Therefore, many additional infants would need to be recruited for this study to look for a replication of these findings.

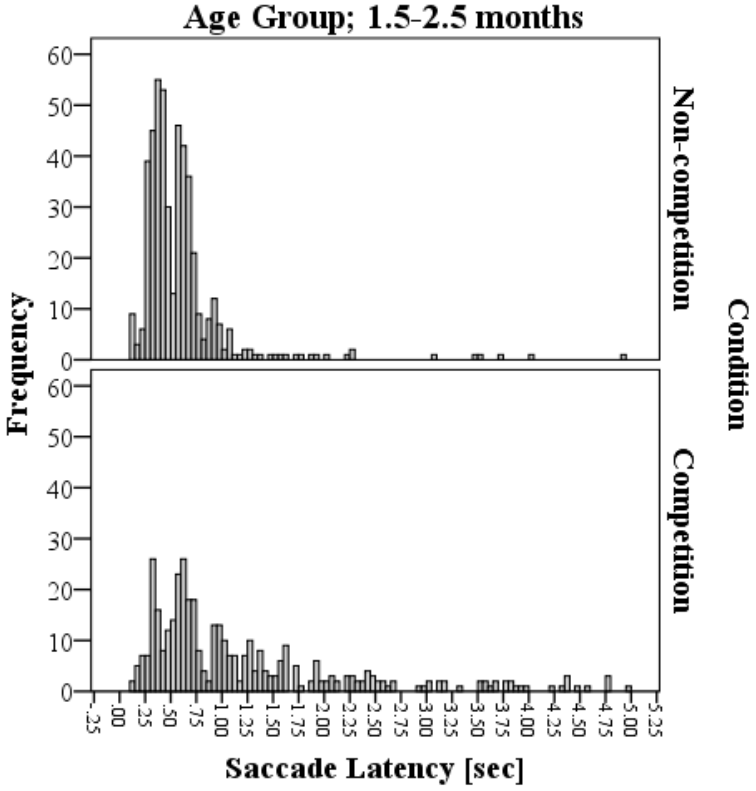
Double target conditions showed similar effects as single target conditions, suggesting that they may have a similar diagnostic value. It would therefore be

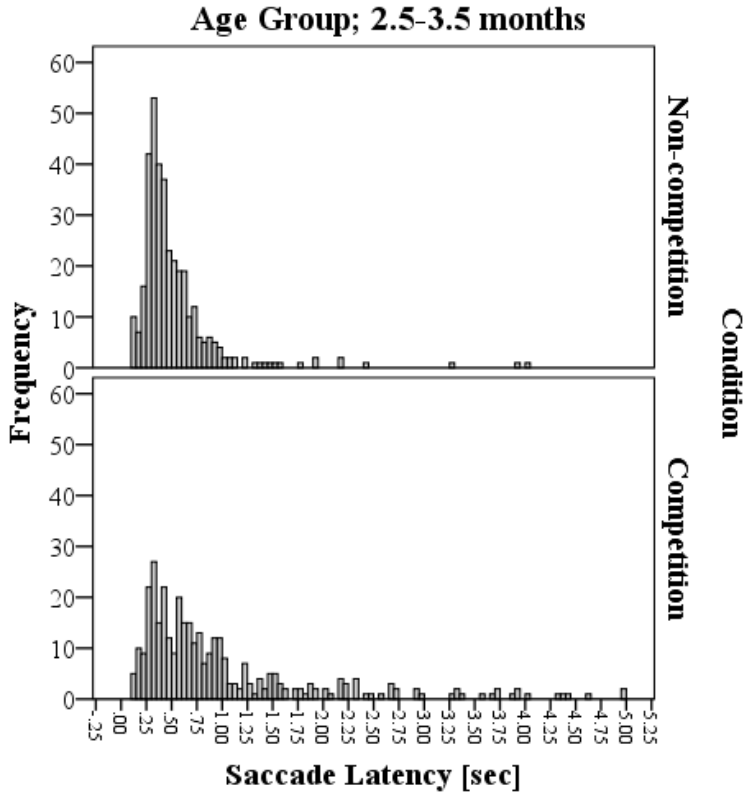
preferable to only use single target conditions for clinical purposes, to decrease the trial number and save testing time.

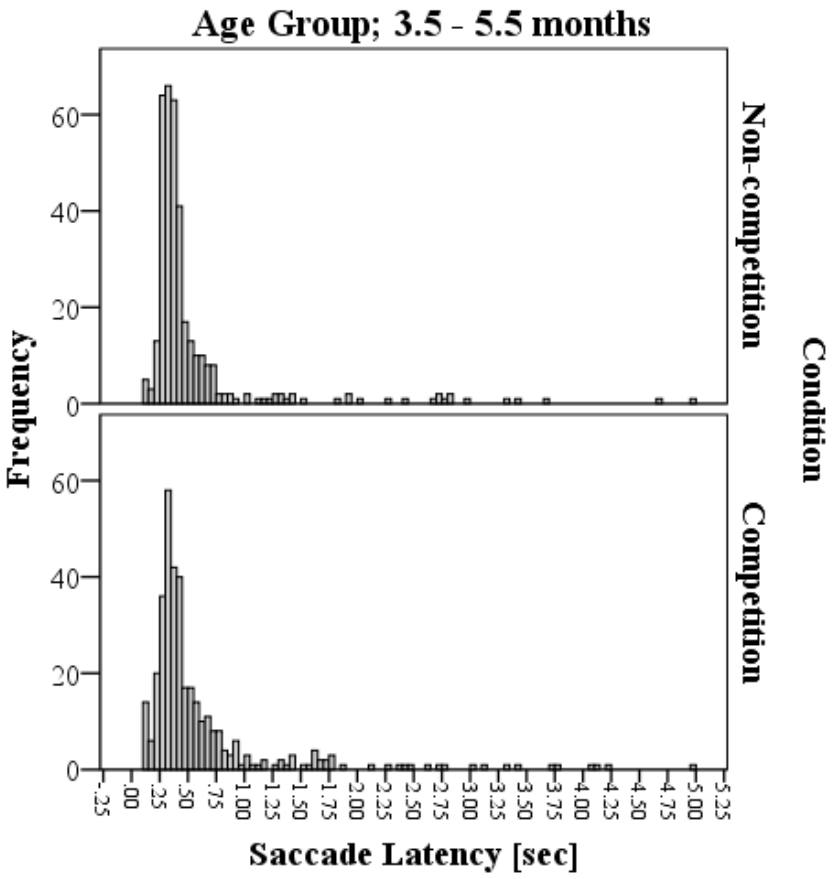
In conclusion, the current pilot study shows that the automated version of combined FSP and eye tracking can be used to monitor development of attention, with possible detection of impairments in disengaging in some mildly preterm-born infants.

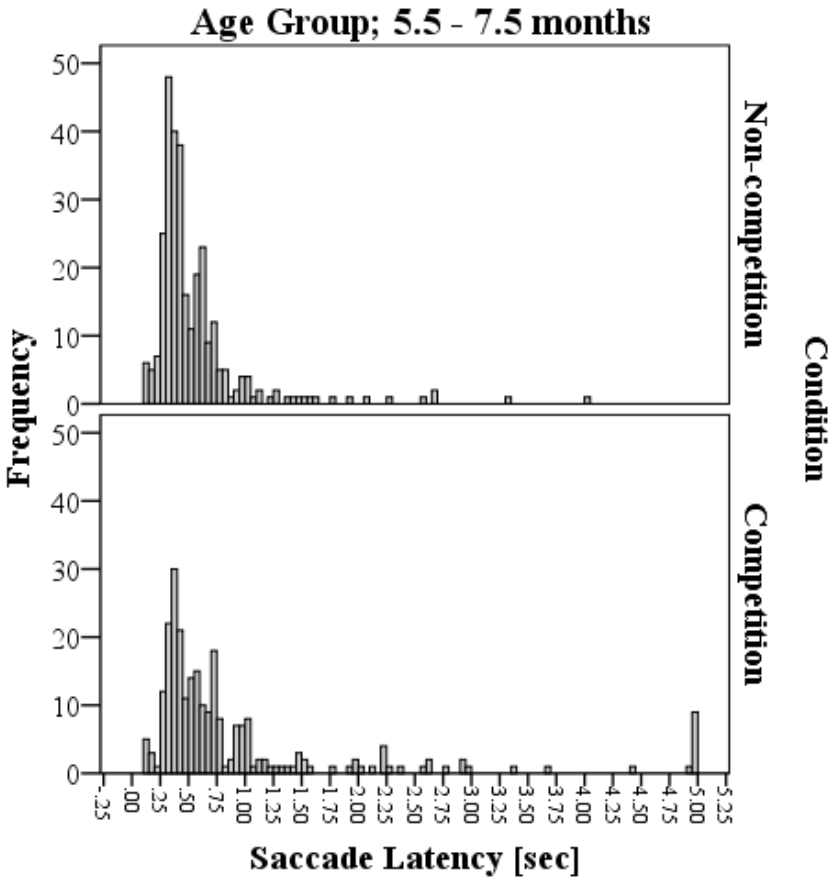
Appendix O. Histograms of the frequency of infants' saccade latencies depending on age group and condition.

The distributions are skewed with the frequency asymptoting towards zero the higher the saccade latency gets.






Age Group; 3.5 - 5.5 months
Frequency
Non-competition
Competition
Condition
Saccade Latency [sec]


Age Group; 5.5 - 7.5 months
Frequency
Non-competition
Competition
Condition
Saccade Latency [sec]

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