Visual Processing Streams:

Interactions, Impairments and Implications for Rehabilitation

Joost Heutink

The research described in this thesis was supported by the Heymans Insitute for Psychological Research and Royal Visio, National Foundation for the Visually Impaired and Blind.

university of groningen

bcn

visio

ISBN: 978-90-367-3226-0

Cover design: Liesbeth Heutink
Illustration: Icon of the All-seeing Eye, Russian, 19th Century.
Printed by Ridderprint Offset Drukkerij B.V., Ridderkerk

Publication of this thesis was financially supported by the University of Groningen and the School of Behavioral and Cognitive Neurosciences (BCN) in Groningen.

RIJKSUNIVERSITEIT GRONINGEN

Visual processing streams: interactions, impairments and implications for rehabilitation

Proefschrift

ter verkrijging van het doctoraat in de
Gedrags- en Maatschappijwetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. F. Zwarts,
in het openbaar te verdedigen op
donderdag 8 november 2007
om 13.15 uur

door

Jochem Helmich Christiaan Heutink
geboren op 28 september 1973
te Zwolle

Promotores:	Prof. Dr. J.M. Bouma
	Prof. Dr. W.H. Brouwer
Beoordelingscommissie:	Prof. Dr. E.H.F. de Haan
	Prof. Dr. A.C. Kooijman
	Prof. Dr. E.J.A. Scherder

Contents

Chapter 1

Outline

Zij weten niet, en verstaan niet,
want het heeft hun ogen bestreken,
dat zij niet zien,
en hun harten,
dat zij niet verstaan.

(Jes. 44:18)

When we open our eyes, we see. When we move our eyes over this page we see letters, words and sentences which we can read and understand. When we look up, a panorama of objects unfolds before us. We are able to visually explore the space surrounding us, identify the faces of people we encounter, and are aware of their facial emotional expressions. Our brain makes sense of the light that enters our eyes. Complex brain mechanisms underlie an ongoing process of seemingly effortless visual perception. This thesis focuses on some of the interactions between these brain mechanisms, specific visual impairments after brain damage and the possibilities for rehabilitation, and the distinction between conscious, overt, visual processing and unconscious, covert, perception.

The present thesis is organized in three sections. Section 1 (*chapter 2*) provides a general overview of the cortical and subcortical brain structures that are involved in visual processing and the way these systems interact. Three visual streams are described: a ventral, occipitotemporal stream for processing information related to specialized recognition of objects and faces; a dorsal, occipitoparietal stream for processing information related to movement, location and motor action; and a subcortical, cortico-amygdalar and thalamo-amygdalar pathway for processing of emotion-related information. Also, some of the most important visual impairments due to brain damage will be discussed.

In section 2 (*chapters 3 and 4*) rehabilitation methods of damage to specific parts of the visual system will be reviewed.

Section 3 (*chapters 5, 6 and 7*) consists of experimental studies that focus on interactions between overt and covert recognition of faces and emotional facial expressions. Finally, *chapter 8* provides a summary of main findings of this thesis, which will be discussed in *chapter 9*.

When damage occurs to a brain structure that is directly or indirectly involved in visual processing, visual perception may become impaired. Visual impairments may affect numerous aspects of functioning in daily life, such as reading, mobility, and recognition of other people. Rehabilitation aims at overcoming the consequences of these impairments, either via restoration or compensation. Both restoration and compensation may operate on a neural, cognitive or behavioural level (Code, 2001).

By far, the most frequently occurring visual disorder after acquired brain injury is a homonymous visual field defect (HVFD). In some patients, the field restores to normal size in the first few months post-injury, while some other patients may adopt a form of scanning strategy, which allows them to compensate for their loss of visual field (Pambakian et al., 2004). However, in most patients spontaneous compensation is absent or insufficient, with severe consequences for activities of daily living (ADL) (Zihl, 1995). Typical complaints of patients with HVFDs are difficulties with reading, and poor detection of people or objects in the contralesional side, leading them to bump into obstacles or people.

In *chapter 3* (Bouwmeester et al., 2007), a systematic review assessing the effects of systematic visual training for patients with HVFDs is presented. Current training methods for HVFDs can be divided into two categories. The first category, vision restoration therapy (VRT), consists of methods aiming at restoration or restitution of a part of the HVFD. VRT aims at increasing the functional visual field by reactivating surviving neurons in the (partially) damaged brain through repeated presentation of light stimuli in the border area of the HVFD. The second category of rehabilitation methods, scanning compensatory therapy (SCT), aims to enlarge the field of search by training patients to make eye movements into their blind hemifield. The objective of the systematic review is to evaluate whether VRT and SCT lead to (1) restoration or restitution of the visual field (i.e. lead to a reduction in the size of the HVFD), (2) an improvement of scanning strategies (i.e. lead to an increase of the size of the visual search field, and (3) an improvement in ADL.

One of the most common and dramatic impairments after damage to the dorsal stream is unilateral spatial neglect. Like patients with HVFDs, neglect patients show poor reading and may ignore objects or people that are located on their contralesional side. The crucial difference with HVFDs though, is that in neglect these symptoms are not caused by a deficient cortical representation of the visual field, but by a deficient representation of attentional and spatial cognition (Robertson & Heutink, 2002).

In *chapter 4* (Robertson & Heutink, 2002) an overview is provided of rehabilitation methods that have been developed during the past decades. Several methods have been clinically evaluated, while other, more recent methods are still experimental. Some of these recent methods nevertheless are of particular interest

since they demonstrate the potential value of interactions between the visual processing streams.

Brain injury affecting the ventral stream for visual processing can result in impaired perception and recognition of faces. Numerous studies have shown that in prosopagnosia, the complete inability to recognize previously familiar faces, covert face recognition may be still preserved (Barton et al., 2001; Barton et al., 2004; Bauer, 1984; De Haan et al., 1987; De Haan et al., 1992; Young et al., 1988). Covert face recognition may reflect processing via dorsal or subcortical brain regions (Bauer, 1984; Gobbini & Haxby, 2007), although other explanations have been put forward as well (De Haan et al., 1992; Farah et al., 1993). In Capgras delusion, which refers to the belief that close acquaintances, such as parents or children, have been replaced by impostors, robots or aliens, overt recognition of faces is intact, while covert recognition is impaired (Ellis et al., 1997; Ellis et al., 2000; Hirstein & Ramachandran, 1997).

In *chapter 5*, a rare case is presented of a woman who displays some characteristics of prosopagnosia and some characteristics of Capgras delusion. In this study, response accuracy, response times and skin conductance response (SCR) to different categories of familiar and unfamiliar faces are assessed to establish whether mechanisms for covert and overt face recognition are intact or impaired.

The past ten years have seen a growing interest in the topic of visual processing of emotional information. In particular, subcortical and cortical processing of facial emotional expressions has been studied. LeDoux' influential model argues that there are two semi-independent pathways for processing emotions (LeDoux, 1996). In this model, the 'low road' receives coarse input directly from the thalamus, allowing fast responses to emotionally significant stimuli. Via the 'high road', the amygdala receives elaborate input from cortical structures. Several neuroimaging studies have shown that activity in the extrastriate cortex is functionally correlated with amygdala activation in response to emotional facial expressions and fear-conditioned faces (Morris et al., 1998; Morris et al., 1999), suggesting an interaction between cortical and subcortical streams that are involved in emotional processing.

In *chapter 6*, a study employing event-related potentials (ERPs) is presented, that investigates early, pre-attentive processing of facial emotional expressions and fear-conditioned faces.

In *chapter 7*, a male patient with a right-amygdala lesion is presented. This patient has impaired overt recognition of facial emotional expressions. In particular, he is unable to tell the difference between an anxious facial expression and a surprised facial expression. Employing ERPs, processing of emotional facial expressions and fear-conditioned faces is assessed. The results are interpreted in terms of covert and overt processing of emotion-related visual input via cortical and subcortical brain structures.

Finally, in *chapter 8*, the results of the different studies in this thesis are summarized, while in *chapter 9* these results are compared and discussed in the light of interactions between the visual processing streams, distinctions between overt and covert visual processing and prospects for rehabilitation.

References

Barton, J. J., Cherkasova, M., & O'Connor, M. (2001). Covert recognition in acquired and developmental prosopagnosia. *Neurology, 57,* 1161-1168.

Barton, J. J., Cherkasova, M. V., & Hefter, R. (2004). The covert priming effect of faces in prosopagnosia. *Neurology, 63,* 2062-2068.

Bauer, R. M. (1984). Autonomic recognition of names and faces in prosopagnosia: a neuropsychological application of the Guilty Knowledge Test. *Neuropsychologia, 22,* 457-469.

Bouwmeester, L., Heutink, J., & Lucas, C. (2007). The effect of visual training for patients with visual field defects due to brain damage: a systematic review. *Journal of Neurology, Neurosurgery and Psychiatry, 78,* 555-564.

Code, C. (2001). Multifactorial processes in recovery from aphasia: developing the foundations for a multileveled framework. *Brain and Language, 77,* 25-44.

De Haan, E. H. F., Bauer, R. M., & Greve, K. W. (1992). Behavioural and physiological evidence for covert face recognition in a prosopagnosic patient. *Cortex, 28,* 77-95.

De Haan, E. H. F., Young, A., & Newcombe, F. (1987). Face Recognition Without Awareness. *Cognitive Neuropsychology, 4,* 385-415.

Ellis, H. D., Lewis, M. B., Moselhy, H. F., & Young, A. W. (2000). Automatic without autonomic responses to familiar faces: Differential components of covert face recognition in a case of Capgras delusion. *Cognitive Neuropsychiatry, 5,* 255-269.

Ellis, H. D., Young, A. W., Quayle, A. H., & De Pauw, K. W. (1997). Reduced autonomic responses to faces in Capgras delusion. *Proceedings of the Royal Society B: Biological Sciences, 264,* 1085-1092.

Farah, M. J., Oreilly, R. C., & Vecera, S. P. (1993). Dissociated Overt and Covert Recognition As An Emergent Property of A Lesioned Neural-Network. *Psychological Review, 100,* 571-588.

Gobbini, M. I. & Haxby, J. V. (2007). Neural systems for recognition of familiar faces. *Neuropsychologia, 45,* 32-41.

Hirstein, W. & Ramachandran, V. S. (1997). Capgras syndrome: a novel probe for understanding the neural representation of the identity and familiarity of persons. *Proceedings of the Royal Society B: Biological Sciences, 264,* 437-444.

LeDoux, J. E. (1996). *The Emotional Brain*. New York: Touchstone.

Morris, J. S., Friston, K. J., Buchel, C., Frith, C., Young, A. W., Calder, A. J. et al. (1998). A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain, 121,* 47-57.

Morris, J. S., Öhman, A., & Dolan, R. J. (1999). A subcortical pathway to the right amygdala mediating "unseen" fear. *Proceedings of the National Academy of Sciences of the United Stated of America, 96,* 1680-1685.

Pambakian, A. L., Mannan, S. K., Hodgson, T. L., & Kennard, C. (2004). Saccadic visual search training: a treatment for patients with homonymous hemianopia. *Journal of Neurology, Neurosurgery and Psychiatry, 75,* 1443-1448.

Robertson, I. H. & Heutink, J. (2002). Rehabilitation of unilateral neglect. In W.H.Brouwer, A. H. van Zomeren, I. J. Berg, J. M. Bouma, & E. H. F. de Haan (Eds.), *Neuropsychological rehabilitation: a cognitive approach* Amsterdam: Boom.

Young, A. W., Hellawell, D., & De Haan, E. H. F. (1988). Cross-Domain Semantic Priming in Normal Subjects and A Prosopagnosic Patient. *Quarterly Journal of Experimental Psychology Section A-Human Experimental Psychology, 40,* 561-580.

Zihl, J. (1995). Visual scanning behavior in patients with homonymous hemianopia. *Neuropsychologia, 33,* 287-303.

Section 1

Introduction

Chapter 2

General introduction: hierarchy, segregation and integration of visual processing streams

The visual system is the dominant sensory system in humans. It is estimated that nearly 30% of the human cortical surface represents information that is predominantly visual (Van Essen, 2004). Over the past few decades, knowledge of the human visual system has accumulated significantly thanks to animal studies (mainly in macaque and cats), lesion studies in humans, and neuroimaging studies employing PET and fMRI.

Not only the degree of involvement in visual processing differs between brain regions, there is also considerable diversity in the type of visual information that is processed in each region. This chapter will give a general (but not exhaustive) overview of the cortical and subcortical brain structures that are involved in visual processing and the way these systems interact. The visual information that we perceive can be roughly divided into three categories or streams. One stream is concerned with perception of physical attributes of objects, one stream is more involved in visuospatial processing, and one is involved in the processing of emotional content (Figure 2.1).

2.1 Visual processing streams

2.1.1 Subcortical and cortical systems for visual processing

Visual processing sets off with the transduction of light into electrical signals in retinal photoreceptors. These electrical signals leave the eye through so-called ganglion cells, which project mainly to the dorsal Lateral Geniculate Nucleus (LGN) of the thalamus, but also to the pulvinar region of the thalamus and the superior colliculus (SC), which lies on the roof of the midbrain and is important for the regulation of eye and head movements (Sommer & Wurtz, 2004). From the LGN, the signal is projected to the primary visual cortex (V1), at which point the first stages of cortical visual processing take place. From V1, the signal travels to more anterior sub-regions of the visual cortex (V2-V8), which are all extensively interconnected areas that contain specialized maps of the visual field. Apart from receiving input from the LGN, V1 also obtains input from the pulvinar and SC – albeit to a lesser extent.

Only 5-10% of the input to geniculate relay cells derives from the retina, which is the driving input. The remaining 90-95% mainly consists of descending inputs from the visual cortex, and ascending inputs from the brainstem. The LGN is

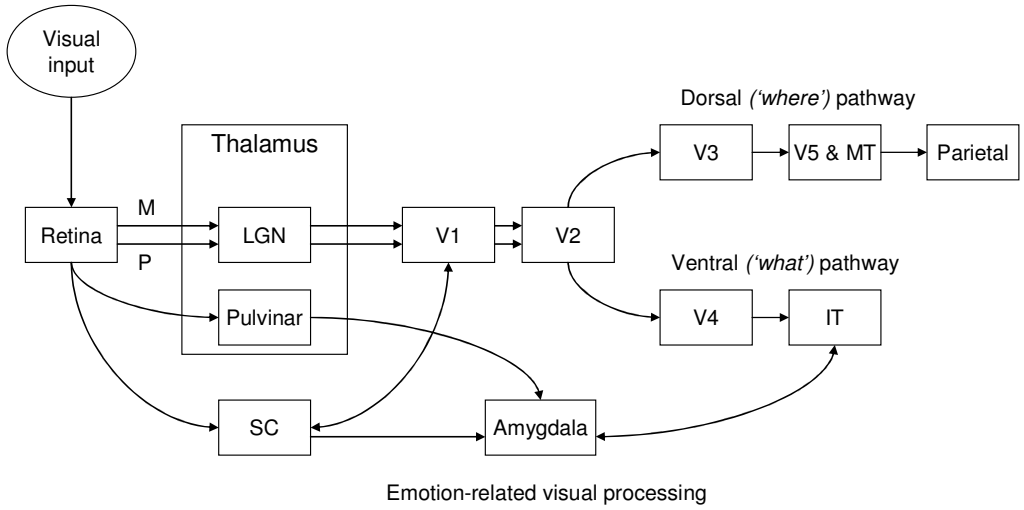


Figure 2.1. Schematic outline of the main pathways involved in visual processing. Only a select few number of connections are shown, and the intrinsic organization of structures is ignored. Visual signals are sent from the retina to the Lateral Geniculate Nucleus (LGN) of the thalamus. From the LGN, signals are projected to area V1 of the visual cortex. The dorsal pathway comprises of V2, V3, V5, medial temporal area (MT) of the superior temporal sulcus, and the parietal cortex. The ventral pathway consists of V2, V4 and the inferior temporal sulcus (IT). The superior colliculus (SC) receives afferent projections from the retina and the visual cortex, and projects visual information to the cortex and the amygdala. The amygdala is the hub in the network for emotion-related processing as it receives input from the pulvinar, SC and IT.

the primary source of input for the visual cortex and is therefore regarded as a 'first order' nucleus. By contrast, the pulvinar region and the SC can be regarded as 'higher order' nuclei, since they are primarily involved in relaying information from one cortical area to another (Sherman & Guillery, 2002), and project less visual information to V1 than the LGN.

A large proportion of visual information is processed in a sequential fashion. That is, through successive stages of processing, input is transformed into a higher-order presentation (Ungerleider & Pasternak, 2004). This 'bottom-up' process starts off with low level input from the retina to the LGN, and in each following step a more

specialized or more elaborate form of processing is performed. However, visual processing is not only a simple matter of successive elaboration of information from lower-order to higher-order areas. At all stages, connections in the visual cortex are reciprocal (Van Essen et al., 1992). Area A, that receives feedforward information from adjacent area B, also provides feedback projections to area B. Feedforward projections provide bottom-up, sensory-driven input to subsequent visual areas, allowing preferential access of biologically relevant or highly salient information. Feedback projections, on the other hand may allow top-down modulation of early visual processing that is the underlying mechanism of selective attention.

Cortical and subcortical systems for visual processing also have elaborate feedback and feedforward projections that allow the different systems to modulate each other, dependent on specific demands of the task that is being performed. The role of the thalamus in visual processing is not merely conveying information from the periphery to the cortex. The thalamus also has a modulatory role in cortico-cortical interactions and subcortico-cortical interactions (Sherman & Guillery, 1996). Visual processing can thus be regarded as a 'quasi-hierarchy' rather than a 'pure' hierarchy (Felleman & Van Essen, 1991).

2.1.2 Subcortical segregation of visual information

Already at the stage of the retina, functional segregation of visual input takes place. Three types of ganglion cells are thought to be involved in visual perception: the so-called M (magnocellular), P (parvocellular) and K (koniocellular) streams (Hendry & Reid, 2000; Irvin et al., 1993; Xu et al., 2001). P cells have a small receptive field and mainly participate in the analysis of form and colour (Livingstone & Hubel, 1988). Cells of the magnocellular (M) system have a larger receptive field and are sensitive to depth, indifferent to colour, and well-suited for the analysis of moving stimuli (Livingstone & Hubel, 1988). Cells in the parvocellular pathway are sensitive to red and green opponency, and convey fine spatial detail. The koniocellular system is indifferent to shape or depth, and primarily conveys information concerning blue-yellow opponency (Dacey & Lee, 1994). Although M, P and K cells have different response characteristics and each handle different aspects of visual information, there is overlap in the type of visual stimuli to which they are activated (Irvin et al., 1993; Kaplan, 2004).

The fibres of the optic nerve, carrying the impulses from the retina, cross over at the optic chiasm in a very specific manner. Visual information that originates at the nasal part of the retina crosses over to the contralateral hemisphere, while visual information origination in the temporal part of the retina passes on to the ipsilateral hemisphere. In this way, visual information from the left visual field of both eyes ends up in the right hemisphere and information from the right visual field is processed by the left hemisphere.

After the optic chiasm, visual information is projected to the LGN via the optic tract, which consists of six different layers that are stacked upon one another. The six layers are arranged in two major divisions and are numbered from the bottom (1) to the top (6). Layers 1 and 2 consist of magnocellular layers, and layers 3 – 6 consist of parvocellular layers. The Koniocellular ganglion cells have only been discovered recently and are thought to project to the regions between each layer of the LGN (Kaplan, 2004). Apart from the division between parvocellular layers and magnocellular layers, there is a division between input from the ipsilateral eye and the contralateral eye. Layers 5, 3 and 2 receive input from the ipsilateral eye, while layers 6, 4 and 1 are innervated by the contralateral eye.

2.1.3 Cortical segregation of visual information: the dorsal and ventral stream

The different streams of visual information are projected in a parallel fashion from the LGN towards V1. The visual cortex of each hemisphere receives input from the contralateral visual field through the optic radiation. In the primary visual cortex, the visual field is represented in such a way that adjacent points in the visual field are represented at adjacent points in the cortex. Therefore, cortical representation of the visual field is also referred to as a topographical map.

From the primary visual cortex, two functionally different pathways are thought to exist: an occipitoparietal stream, also called the ‘dorsal’ route, and an occipitotemporal stream, also called the ‘ventral’ route (Haxby et al., 1991; Mishkin et al., 1983; Ungerleider & Mishkin, 1982).

The ventral, or ‘what’, pathway receives input from the P stream of the LGN projecting to V1 (Livingstone & Hubel, 1988), and is involved in processing of form, texture and colour, which are of crucial importance to the perception of objects. The ventral pathway originates at V1 and projects through V2 and V4 to specific areas in the inferior temporal cortex (IT), the angular gyrus, and limbic structures such as the

hippocampus and the amygdala (Ungerleider & Pasternak, 2004). Processing visual information forward along the ventral pathway, there is a general trend towards selectivity for increasingly complex stimulus features or combinations of features.

The dorsal, or 'where' pathway, receives its initial input from the M stream of the LGN projecting to V1 (Livingstone & Hubel, 1988), and is involved in visuospatial analysis, the localization of objects in visual space, and the modulation of visual guidance to movements towards these objects. The dorsal pathway originates at V1 and projects through V2 and V3 to V5. From there, the information is passed on to additional areas in the parietal cortex, the middle temporal area and the superior temporal cortex (Ungerleider & Pasternak, 2004).

Although the ventral and dorsal pathways process different aspects of the visual environment, the information that is carried by each of the two pathways needs to be integrated to allow visually guided behaviour. Therefore, extensive connections between the two streams exist, that allow some aspects of this integration to take place within each stream (Ungerleider & Pasternak, 2004). In addition, the dorsal and ventral streams have reciprocal connections to regions that are situated beyond the visual areas of the cortex and that are not modality-specific. For instance, in several cortical and subcortical brain regions, visual information is integrated with tactile input. These regions include the parietal cortex, superior temporal sulcus, superior colliculus, and putamen (Bruce et al., 1981; Graziano & Gross, 1995; Graziano & Gross, 1998; Hyvarinen, 1981; Hyvarinen & Poranen, 1974; Stein et al., 1976). Via these multimodal areas, tactual perception can be enhanced by visual information. Moreover, visual input can overrule concurrent tactile input, indicating the dominance of the visual modality over the sensory modality (Ro et al., 2004). We were able to demonstrate this effect in a patient with right-hemisphere damage, who was unable to feel that his hand was being touched when his hand was obscured from view. However, when touch occurred at the same time with a salient (but not predictive) light flash on a rubber hand, placed right above his concealed hand, his tactile sensitivity dramatically improved (Rorden et al., 1999).

2.1.3.1 Cortical Expertise Systems in the ventral stream

Neuroimaging studies indicate that, in addition to a more general-purpose region that responds to any kind of visually presented object, the ventral pathway contains a small number of category-specific regions, which are primarily involved in processing

a specific stimulus class (Kanwisher, 2004). The fusiform face area (FFA), for instance responds selectively to faces compared to other objects (Halgren et al., 1999; Haxby et al., 1999; Kanwisher et al., 1997; McCarthy et al., 1997). The FFA is thought to be primarily involved in the analysis of non-changeable, invariant aspects of faces, while analysis of changeable aspects of faces is preferentially processed by other brain regions (Haxby et al., 2000). For instance, the superior temporal sulcus appears to be involved in gaze direction (Kingstone et al., 2004; Puce et al., 1998), while the middle temporal gyrus is implicated in cortical processing of facial emotional expressions (Critchley et al., 2000).

Although the FFA may respond selectively to faces, this does not mean that it responds exclusively to faces. For instance, the FFA is also activated by cars in car fanatics (Gauthier et al., 1999). Gauthier and colleagues showed that recognizing novel stimuli called 'Greebles', also activated the FFA, which lead them to argue that the FFA is specialized for discriminating between any structurally similar exemplars of a given category for which the subject is an expert (Tarr & Gauthier, 2000). However, evidence from neurological patients indicates that different cortical mechanisms may be involved in the recognition of faces and 'objects-of-expertise'. For instance, there is a report of a farmer that was impaired at recognizing human faces due to brain damage while being less impaired at recognizing the animals of his flock (Mcneil & Warrington, 1993). Oppositely, another farmer was impaired at recognizing his flock, but was less impaired at recognizing human faces (Assal et al., 1984). Also, a very recent study with dog experts provided further evidence of a dissociation in perception of faces and perception of objects-of-expertise (Robbins & McKone, 2007).

Other 'expertise' brain areas in the ventral stream that are primarily involved in processing specific stimulus classes are the parahippocampal place area (PPA), which responds selectively to information about spatial layouts and places (Epstein & Kanwisher, 1998), and the extrastriate body area (EBA), which is involved in recognizing individuals by their posture and the perception of one's own body parts (Downing et al., 2001). The PPA is located at the parahippocampal cortex and the EBA is found in the right (and sometimes also the left) lateral occipitotemporal cortex, on the lower lip of the superior temporal sulcus, just superior to the middle temporal area.

2.1.4 Subcortical and cortical processing of emotionally relevant information

In the previous section, the cortical segregation of 'what' versus 'where' related visual information originating at the Parvo and Magno streams that project from the retina through the LGN to the visual cortex has been described. In the following paragraph, the brain regions that are primarily involved in the processing of emotion related visual information will be discussed. As mentioned earlier, feedback and feedforward projections between separate brain regions allow bottom-up modulation of hierarchically higher regions and top-down modulation of hierarchically lower areas. There is growing evidence that this is especially the case in the processing of visual information with emotional content.

Emotional processing is crucial for the evolutional survival of species. When we are threatened, our body needs to mobilize all its available resources to take protective action, such as engaging in a fight or withdrawing from the threatening situation (flight). These actions need to be executed instantly, as any delay would increase the risk of sustaining injury or death inflicted by the threat. Since vision is the dominant sensory modality, the visual system must be able to support a quick response to emotionally relevant information. The amygdalae, located anterior to the hippocampus within the medial temporal lobes, are thought to play a crucial role in the neural circuit for emotional processing (Adolphs, 2002; Anderson et al., 2003; Haxby et al., 2002; LeDoux, 2000; Zald, 2003). The amygdalae project to the brainstem in order to generate fear responses, while projections to cortical areas such as the frontal cortex, would allow conscious experience of fear and other cognitive aspects of emotional processing (LeDoux, 1995).

Two semi-independent pathways are thought to underlie the recognition of and response to emotional stimuli in the visual domain (Adolphs, 2002; LeDoux, 2000; Zald, 2003). One pathway appears to be important for quick, instinctive, emotional responses. In a second pathway, emotional information is processed more thoroughly, but also slower. These pathways have also become known as the 'low road' and the 'high road' for emotional processing (Figure 2.2) (LeDoux, 1996; LeDoux, 2002). LeDoux argued that via the 'low road', sensory information about threatening stimuli is directed straight from the thalamus to the amygdala, outside the scope of consciousness. The benefit of this direct route to the amygdala is evident: it allows extremely rapid responses to a potential threat. However, this speed of processing also has its downside. Because the emotional responses generated via the 'low road' are

not based on elaborate (i.e. cortical) processing, but rather on sketchy, low-level input, they are thought to have a high false alarm rate (Büchel & Dolan, 2000), and an inability to differentiate between stimuli with similar, yet distinct, characteristics (LeDoux, 1996), leading to an overgeneralization of responses (Zald, 2003). For that reason, the 'low road' has been labelled as 'quick and dirty' (LeDoux, 1995; LeDoux, 1996; LeDoux, 2002). Apart from generating a quick behavioural response, early thalamo-amygdalar processing of emotional information may also prime the visual cortex pre-attentively to prioritize enhanced higher order processing (Armony & Dolan, 2002; Davidson & Irwin, 1999; Zald, 2003).

Emotional responses that are generated via the 'high road' on the other hand, are thought to be based on cortical projections to the amygdala. Since the source of input comes from specialized higher-order visual areas, such as facial expression-related areas in the middle temporal gyrus (Critchley et al., 2000), which is the human homologue of the superior temporal sulcus (Hasselmo et al., 1989), and in the orbitofrontal cortex (Rolls et al., 2006), the affective response is more fine-tuned to the complexity of the emotional stimulus and its context. However, because processing by these specialized cortical areas is preceded by numerous earlier stages of processing, emotional responses via the 'high road' takes considerably more time than processing via the 'low road'. For this reason, the 'high road' has been qualified as 'slow but accurate'. Thus, subcortical brain structures are continuously involved in the processing of emotionally relevant visual information, allowing rapid ('instinctive') behavioural responses on one hand, and prioritising enhanced, higher order attentive processing of these cues on the other hand (LeDoux, 1996; LeDoux, 2000).

2.2 Damage to the visual system

As we have seen in the previous paragraphs, many brain structures are involved in different stages and types of visual processing. Therefore perceptual and behavioural consequences of damage to these areas depend to a great extent on the location of the lesion. In this paragraph some specific syndromes of impaired visual processing will be discussed.

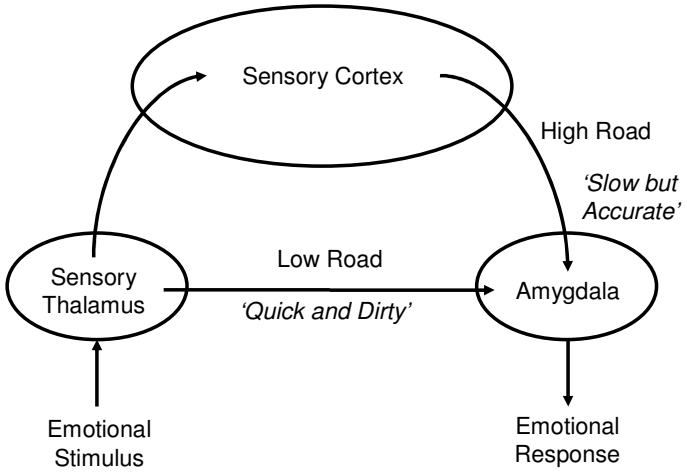


Figure 2.2. LeDoux' model for emotional processing (LeDoux, 1996; LeDoux, 2002). According to this model, the 'low road' allows extremely fast processing of emotional information via a direct projection of the thalamus to the amygdala. When processing occurs via the 'high road', the amygdala receives input via the sensory cortex. The 'low road' is thought to be 'quick and dirty', due to the crude representations of visual information in the thalamus, while the 'high road' is thought to be 'slow but accurate', since detailed, high level input from the sensory cortex is preceded by numerous processing stages.

2.2.1 Damage to the optic pathway

The largest group of visual disorders after acquired brain damage are homonymous visual field defects (HVFDs). Approximately 20% to 30% of all patients with cerebrovascular infarction requiring therapy in a rehabilitation centre have HVFDs (Kerkhoff et al., 1994). Homonymous hemianopia refers to a loss of perception in half the fields of vision, affecting both eyes, due to damage to the visual pathway beyond the optic chiasm. This damage to the visual pathway can occur in the LGN, the optic radiation or the striate cortex in one cerebral hemisphere. Damage to the LGN or optic radiation leads to deficient transmission of visual information, while damage to the striate cortex leads to deficient cortical representation of the visual field. In some patients with hemianopia, the central 5º of vision is not affected by the loss of perception. This phenomenon, called macular sparing, can be explained by the fact that the occipital poles in each hemisphere receive their blood supply from both the

posterior artery and the middle artery. If cerebrovascular infarction affects only the posterior artery, the part of the primary visual cortex in which the central visual is represented is still intact, because it still receives blood supply from the middle cerebral artery. The rest of the primary visual cortex however, which is only provided for by the posterior artery, will be affected. Macular sparing may be of crucial importance for reading ability in patients with HVFDs (Trauzettel-Klosinski, 2002; Trauzettel-Klosinski & Reinhard, 1998).

Partial damage of the optic radiation or the primary visual cortex may lead to quadrantanopia, a condition in which only the upper or lower part of the contralateral visual field is affected. For instance, damage to the lower lip of the calcarine sulcus or the ventral part of the optic radiation lead to upper contralateral hemianopia. When damage is only restricted to an even smaller region of the topographical map, the HVFD is called a scotoma.

2.2.1.1 Residual vision after damage to V1: Blindsight

Although patients with HVFDs due to damage of the primary visual cortex do not have conscious visual experience in the affected part of the visual field, some rudimentary levels of visual processing may be preserved. This phenomenon is called 'blindsight' (Weiskrantz et al., 1974). Although patients with blindsight are unaware of their residual capacity for visual processing, numerous studies showed preserved ability to detect direction of motion, wavelength, stimulus presence, and form (see Weiskrantz (2004), for an overview). Blindsight is most commonly explained by intact visual processing by the subcortical stream, involving the superior colliculus and the pulvinar, either processing crude visual information themselves or projecting to cortical visual areas that are higher in hierarchy than V1.

Following LeDoux' proposed dual route for emotional processing, it can be argued that the subcortical visual pathway should be able to handle emotionally relevant visual stimuli without involvement of the cortex. Evidence for this 'low road' based emotional processing comes from patients with cortical blindness who can reliably discriminate between facial emotional expressions, a condition that is also referred to as 'affective blindsight'. De Gelder et al. reported a patient (G.Y.) who was able to discriminate between facial emotional expressions presented in his right visual field despite a lesion in the left striate cortex (De Gelder et al., 1999). Pegna et al. demonstrated the same phenomenon in a patient with bilateral damage to the visual

cortex and also showed with functional MRI (fMRI) that the right amygdala was activated during the unconscious processing of emotional facial expressions (Pegna et al., 2005). Other studies showed that affective blindsight may also be achieved by aversively conditioned stimuli (Hamm et al., 2003) and that the activity of the amygdala in response to these stimuli is linked with activity in the superior colliculus and pulvinar (Morris et al., 2001).

2.2.2 Damage to the dorsal visual pathway

There are several syndromes that are linked with lesions in the dorsal stream. One of the rarest of these syndromes is akinetopsia, which refers to the loss of perception of visual motion, with other visual functions such as perception of form and colour being intact (Rizzo et al., 1995). Akinetopsia is thought to be caused by bilateral damage of area V5 (Zeki, 1991; Zihl et al., 1983), while unilateral damage to area V5 may lead to more subtle deficits in motion processing or hemiakinetopsia. (Schenk & Zihl, 1997).

A specific set of symptoms which has also been related to impaired visual processing in the dorsal stream is Bálint Syndrome. Bálint Syndrome is classically defined as a triad of simultanagnosia, optic ataxia and oculomotor apraxia (Balint, 1909), although it is questionable whether this combination truly represents a specific clinical entity. Patients with simultanagnosia are unable to identify two items presented simultaneously because they cannot integrate visual information into a global representation of space (Farah, 2004). Dorsal simultanagnosia is most commonly caused by bilateral occipitoparietal damage (Jackson et al., 2006). In optic ataxia, visual guidance of movements towards objects is impaired due to a disconnection between cortical motor systems and visual inputs (Perenin & Vighetto, 1988). In oculomotor apraxia, patients are impaired at making voluntary eye movements from one fixation point to another fixation point in space. The name oculomotor apraxia is confusing, because when patients are not fixating on any object in particular, they are still able to make saccades to a peripheral target (Girkin & Miller, 2001).

Probably the best-known disorder related to impaired dorsal processing is unilateral neglect, which can be described as a failure, difficulty or slowness in reporting, interacting with or moving towards objects, sounds or representations as a consequence of their spatial position, most frequently on the left. Although both left

and right hemisphere stroke patients may suffer from neglect in the acute phase (De Kort, 1996), chronic neglect is almost exclusively caused by right hemisphere lesions (Bisiach & Vallar, 1988; Vallar, 1993). One of the striking aspects of neglect is that it can be caused by a variety of brain regions, which are all part of a complex network that is involved in the modulation of spatial attention. These brain regions include the inferior parietal lobe, the middle temporal lobe, the superior temporal lobe and subcortical areas such as the basal ganglia and the thalamus (for an overview, see Robertson & Halligan, 1999). Another deficit in which patients are worse at detecting items presented at the contralesional side compared to the ipsilesional side is double simultaneous extinction. Patients with extinction are unaware of briefly presented stimuli on the contralesional side when there is another stimulus presented simultaneously at the ipsilesional side (Mattingley et al., 1997). Like unilateral neglect, extinction may be caused by various brain lesions, although it is most often caused by focal parietal lesions that leave primary sensory pathways intact (Driver & Vuilleumier, 2001)

2.2.2.1 Interactions between the dorsal, ventral and subcortical streams may overcome neglect and visual extinction

As described earlier, there are extensive connections between the dorsal and ventral streams, which allow us to make visually guided motor actions. In a series of experiments, Robertson and colleagues showed that the spatial bias in neglect patients can be altered by changing the purpose of a specific motor action. In these experiments, neglect patients were first instructed to point to the centre of a metal rod, which resulted in a significant bias towards the right. When asked to reach for the rod with a pincer grip of forefinger and thumb, the perceived middle was significantly further to the left (Robertson et al., 1995; Robertson et al., 1997).

Perhaps even more striking are the interactions between the visual pathway for emotionally relevant information and the dorsal stream that have been demonstrated by Vuilleumier and colleagues. In a series of experiments, they showed that patients with neglect and visual extinction were better at detecting emotionally significant stimuli (such as images of spiders and angry faces) than emotionally neutral stimuli (such as images of flowers and faces with a neutral expression) that were presented in contralesional space (Vuilleumier & Schwartz, 2001a; Vuilleumier & Schwartz, 2001b). These results indicate that some impairments caused by damage to the dorsal

stream, such as impaired visuospatial processing, visually guided behaviour and localization of objects, may be altered or overcome via interactions with the ventral and subcortical pathways.

2.2.3 Damage to the ventral visual pathway

A number of clinical syndromes are related to occipitotemporal brain lesions. Most of these syndromes are a distinct form of visual agnosia. Visual agnosia is defined as impaired recognition of objects which is not caused by a sensory deficit or generalized intellectual loss (Farah, 1992). Visual agnosias are often divided into two groups: apperceptive agnosia and associative agnosia. Patients with apperceptive agnosia are unable to perceive an object because visual information is not integrated into a global percept, leading to so-called piecemeal perception. In severe cases, apperceptive visual agnosia leads to impaired matching, copying and recognizing of basic shapes (Farah, 2004). Because apperceptive agnosia is usually associated with posterior brain lesions, many patients have HVFDs as well, but these are insufficient to explain the perceptual impairment. Patients with associative agnosia, on the other hand, have intact global perception of visual information and are able to match and copy shapes, but are unable to identify objects or categories of objects (Farah, 2004). Associative agnosias are thought to be either the result of occipitotemporal lesions that cause a disconnection between areas responsible for basic visual perception and memory systems involved in object recognition or the result of a deficit of perception of a specific category of visual forms, such as faces, objects or words (Catani & ffytche, 2005).

One type of agnosia, specifically limited to reading disorders, is *pure alexia*. Patients with pure alexia have severely impaired recognition of single-word forms, but are still able to read letter-by-letter. Patients with pure alexia may not recognize the word “hat”, but by spelling the letters “h”, “a” and “t” aloud they are still capable of (extremely) slow reading. Their deficit is attributed to damage to a specific area located at the left mid fusiform gyrus, the Visual Word Form Area (VWFA), or a disconnection between the primary visual cortex and the VWFA (e.g. due to callosal damage). This area is highly specialized in whole-word recognition, which allows skilled readers to recognize seven-letter words as quickly as three-letter words (McCandliss et al., 2003), although it is subject to debate whether the VWFA also responds to other visual input types (Kleinschmidt & Cohen, 2006; Price & Devlin,

2003). Interestingly, Maher et al. described a patient with pure alexia due to a large occipital infarction, who increased reading speed dramatically (from 20 words to 44 words/min) by 'copying' the letters in the palm of her hand (Maher et al., 1998). This indicates that although stored representation could not be accessed via the ventral stream for visual processing, motor activity and tactile feedback caused by copying allowed access to these representations via the dorsal stream.

Another specific type of agnosia is *prosopagnosia* – the inability to recognize previously familiar faces or to learn new faces (Damasio, 1985). Impaired recognition is specifically limited to faces, since patients are still able to recognize their family and friends relying on posture, voice or specific clothes. Most patients with prosopagnosia have bilateral damage to the inferior occipitotemporal cortex, in particular the lingual and fusiform gyri (Damasio et al., 1982; Damasio, 1985), but there are also numerous reports of prosopagnosia after unilateral right-hemisphere lesions (DeRenzi et al., 1994). There is a good deal of evidence that although prosopagnosia patients have severely impaired explicit recognition of familiar faces (i.e. they are unable to tell the difference between familiar and unfamiliar faces), implicit or covert face recognition may still be intact. For instance, prosopagnosia patients show enhanced skin conductance responses (SCRs) to familiar faces compared to unfamiliar faces (Bauer, 1984; Tranel et al., 1995). This dissociation between impaired overt and preserved covert face recognition has also been established in behavioural experiments, such as tasks involving face-name associations (De Haan et al., 1987; De Haan et al., 1991) and priming tasks (Barton et al., 2004; Young et al., 1988). It has been suggested that covert face recognition reflects visual processing via other visual processing routes such as the dorsal stream or the subcortical, emotion-related, stream (Bauer, 1984; Gobbini & Haxby, 2007). There are also other explanations, such as a disconnection between an intact face recognition system and the processes that signal recognition to an awareness system (De Haan et al., 1992). Also, it could be the case that covert recognition merely reflects residual activation of an impoverished rather than completely damaged system for face recognition (Farah et al., 1993). Which of these explanations is closest to the true nature of the dissociation between covert and overt face recognition is still unclear (Schweinberger & Burton, 2003).

2.2.4 Damage to the cortical and subcortical pathway for emotional processing

Various studies before the 1990s found that patients with right-hemisphere damage have more impaired visual emotion-related processing than left-hemisphere patients. Especially performance on tasks that involve discriminating, naming or grouping of emotional scenes or facial emotional expressions were found to be impaired in right-hemisphere patients (Cicone et al., 1980; DeKosky et al., 1980; Etcoff, 1984; Kolb & Taylor, 1981). More recently, the role of damage to the amygdala in impaired emotional processing has been investigated. From these studies it has become clear that bilateral damage to the amygdala leads to impaired recognition of facial expressions that are related to negative emotions. In most cases, recognition of fear is impaired (Adolphs et al., 1994; Adolphs et al., 1999; Schmolck & Squire, 2001; Wang et al., 2003), and less frequently recognition of sadness and anger (Adolphs et al., 1999; Adolphs & Tranel, 2004; Schmolck & Squire, 2001; Scott et al., 1997). The consequences of unilateral amygdala damage appear to be less severe, as recognition of basic emotional expressions may be unimpaired (Adolphs et al., 1998), although impairments have been found on tasks involving conditioning (LaBar et al., 1995), recognition of complex emotional expressions (Adolphs et al., 2002) and emotional scenes (Adolphs & Tranel, 2003). There is some evidence that patients with left-amygdala lesions have more impairments on tasks that involve a combination of emotional and verbal or language-related processing (Buchanan et al., 2001; Frank & Tomaz, 2003; Funayama et al., 2001). Right-amygdala patients may be more impaired at tasks that are related to visual processing of emotional information without verbal processing, such as viewing pictures (Funayama et al., 2001) or emotional scenes (Adolphs & Tranel, 2003).

It is unclear whether impaired recognition of facial expressions after amygdala damage may be compensated for or overcome by facial processing via the ventral or dorsal routes for visual processing. As described earlier, in prosopagnosia, a dissociation is found between impaired covert and intact overt face recognition. There is ample evidence that overt, explicit, recognition of facial emotional expressions is impaired in patients with amygdala damage. However, it is not clear whether some level of covert recognition, possibly via the dorsal or ventral streams may be still intact in these patients.

2.3 Summary

In the previous sections, three pathways for visual processing were described. Each pathway is dedicated to the processing of a specific class of information. The dorsal ('where') stream is primarily involved in the analysis of movement and the location of objects in space. The ventral ('what') stream is specialized in the perception of form and colour. For processing of emotionally significant visual information, the involvement of subcortical structures, particularly the amygdala, is essential.

Within each stream, visual input is processed in a quasi-hierarchical manner. This hierarchy can be based on increasing selectivity for specific stimuli, as is seen in the ventral stream, or decreasing modality-specific processing, as can be seen in the dorsal stream. However, reciprocal connections exist both within each stream and between the three streams. In normal visual processing, these connections allow complex visuomotor behaviour, visuosensory integration, and task-dependent top-down or stimulus-dependent bottom-up processing of information. When parts of the cerebral visual system are damaged, interconnections between streams may help to overcome specific aspects of impaired vision.

References

Adolphs, R. (2002). Neural systems for recognizing emotion. *Current Opinion In Neurobiology, 12,* 169-177.

Adolphs, R., Baron-Cohen, S., & Tranel, D. (2002). Impaired recognition of social emotions following amygdala damage. *Journal of Cognitive Neuroscience, 14,* 1264-1274.

Adolphs, R. & Tranel, D. (2003). Amygdala damage impairs emotion recognition from scenes only when they contain facial expressions. *Neuropsychologia, 41,* 1281-1289.

Adolphs, R. & Tranel, D. (2004). Impaired judgments of sadness but not happiness following bilateral amygdala damage. *Journal of Cognitive Neuroscience, 16,* 453-462.

Adolphs, R., Tranel, D., & Damasio, A. R. (1998). The human amygdala in social judgement. *Nature, 393,* 470-474.

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. R. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature, 372,* 669-672.

Adolphs, R., Tranel, D., Hamann, S., Young, A. W., Calder, A. J., Phelps, E. A. et al. (1999). Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia, 37,* 1111-1117.

Anderson, A. K., Christoff, K., Panitz, D., De Rosa, E., & Gabrieli, J. D. E. (2003). Neural correlates of the automatic processing of threat facial signals. *Journal of Neuroscience, 23,* 5627-5633.

Armony, J. L. & Dolan, R. J. (2002). Modulation of spatial attention by fear-conditioned stimuli: an event-related fMRI study. *Neuropsychologia, 40,* 817-826.

Assal, G., Favre, C., & Anderes, J. P. (1984). Non-Recognition of Familiar Animals by A Farmer - Zooagnosia Or Prosopagnosia for Animals. *Revue Neurologique, 140,* 580-584.

Balint, R. (1909). Seelenlähmung des 'Schauens', optische Ataxie, räumliche Störung der Aufmerksamkeit. *Monatsschrift für Psychiatrie und Neurologie, 25,* 51-81.

Barton, J. J., Cherkasova, M. V., & Hefter, R. (2004). The covert priming effect of faces in prosopagnosia. *Neurology, 63,* 2062-2068.

Bauer, R. M. (1984). Autonomic recognition of names and faces in prosopagnosia: a neuropsychological application of the Guilty Knowledge Test. *Neuropsychologia, 22,* 457-469.

Bisiach, E. & Vallar, G. (1988). Hemineglect in humans. In F.Boller & J. Grafman (Eds.), *Handbook of neuropsychology (Vol. 1)* (pp. 195-222). Amsterdam: Elsevier.

Bruce, C., Desimone, R., & Gross, C. G. (1981). Visual properties of neurons in a polysensory area in superior temporal sulcus of the macaque. *Journal of.Neurophysiology, 46,* 369-384.

Buchanan, T. W., Denburg, N. L., Tranel, D., & Adolphs, R. (2001). Verbal and nonverbal emotional memory following unilateral amygdala damage. *Learning and Memory, 8,* 326-335.

Büchel, C. & Dolan, R. J. (2000). Classical fear conditioning in functional neuroimaging. *Current Opinion In Neurobiology, 10,* 219-223.

Catani, M. & ffytche, D. H. (2005). The rises and falls of disconnection syndromes. *Brain, 128,* 2224-2239.

Cicone, M., Wapner, W., & Gardner, H. (1980). Sensitivity to emotional expressions and situations in organic patients. *Cortex, 16,* 145-158.

Critchley, H., Daly, E., Phillips, M., Brammer, M., Bullmore, E., Williams, S. et al. (2000). Explicit and implicit neural mechanisms for processing of social information from facial expressions: a functional magnetic resonance imaging study. *Human Brain Mapping, 9,* 93-105.

Dacey, D. M. & Lee, B. B. (1994). The 'blue-on' opponent pathway in primate retina originates from a distinct bistratified ganglion cell type. *Nature, 367,* 731-735.

Damasio, A. R. (1985). Prosopagnosia. *Trends in Neurosciences, 8,* 132-135.

Damasio, A. R., Damasio, H., & Vanhoesen, G. W. (1982). Prosopagnosia - Anatomic Basis and Behavioral Mechanisms. *Neurology, 32,* 331-341.

Davidson, R. J. & Irwin, W. (1999). The functional neuroanatomy of emotion and affective style. *Trends in Cognitive Sciences, 3,* 11-21.

De Gelder, B., Vroomen, J., Pourtois, G., & Weiskrantz, L. (1999). Non-conscious recognition of affect in the absence of striate cortex. *Neuroreport, 10,* 3759-3763.

De Haan, E. H. F., Bauer, R. M., & Greve, K. W. (1992). Behavioural and physiological evidence for covert face recognition in a prosopagnosic patient. *Cortex, 28,* 77-95.

De Haan, E. H. F., Young, A., & Newcombe, F. (1987). Face Recognition Without Awareness. *Cognitive Neuropsychology, 4,* 385-415.

De Haan, E. H. F., Young, A. W., & Newcombe, F. (1991). Covert and overt recognition in prosopagnosia. *Brain, 114 (Pt 6),* 2575-2591.

De Kort, P. (1996). *Neglect, een klinisch onderoek naar halfzijdige verwaarlozing bij patienten met een cerebrale bloeding of infarct.* RijksUniversiteit Groningen.

DeKosky, S. T., Heilman, K. M., Bowers, D., & Valenstein, E. (1980). Recognition and discrimination of emotional faces and pictures. *Brain and Language, 9,* 206-214.

DeRenzi, E., Perani, D., Carlesimo, G. A., Silveri, M. C., & Fazio, F. (1994). Prosopagnosia can be associated with damage confined to the right hemisphere--an MRI and PET study and a review of the literature. *Neuropsychologia, 32,* 893-902.

Downing, P. E., Jiang, Y. H., Shuman, M., & Kanwisher, N. (2001). A cortical area selective for visual processing of the human body. *Science, 293,* 2470-2473.

Driver, J. & Vuilleumier, P. (2001). Perceptual awareness and its loss in unilateral neglect and extinction. *Cognition, 79,* 39-88.

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

Etcoff, N. L. (1984). Perceptual and conceptual organization of facial emotions: hemispheric differences. *Brain and Cognition, 3,* 385-412.

Farah, M. J. (1992). Agnosia. *Current Opinion In Neurobiology, 2,* 162-164.

Farah, M. J. (2004). *Visual agnosia*. (2 ed.) Cambridge (MA): The MIT Press.

Farah, M. J., Oreilly, R. C., & Vecera, S. P. (1993). Dissociated Overt and Covert Recognition As An Emergent Property of A Lesioned Neural-Network. *Psychological Review, 100,* 571-588.

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

Frank, J. E. & Tomaz, C. (2003). Lateralized impairments of the emotional enhancement of verbal meomory in patients with amygdala-hippocampus lesion. *Brain and Cognition, 52,* 223-230.

Funayama, E. S., Grillon, C., Davis, M., & Phelps, E. A. (2001). A double dissociation in the affective modulation of startle in humans: effects of unilateral temporal lobectomy. *Journal of Cognitive Neuroscience, 13,* 721-729.

Gauthier, I., Tarr, M. J., Anderson, A. W., Skudlarski, P., & Gore, J. C. (1999). Activation of the middle fusiform 'face area' increases with expertise in recognizing novel objects. *Nature Neuroscience, 2,* 568-573.

Girkin, C. A. & Miller, N. R. (2001). Central disorders of vision in humans. *Survey in Ophthalmology, 45,* 379-405.

Gobbini, M. I. & Haxby, J. V. (2007). Neural systems for recognition of familiar faces. *Neuropsychologia, 45,* 32-41.

Graziano, M. S. & Gross, C. G. (1995). The representation of extrapersonal space: A possible role for bimodal, visual-tactile neurons. In M.S.Gazzaniga (Ed.), *The cognitive neurosciences* (pp. 1021-1034). Cambridge (MA): MIT Press.

Graziano, M. S. & Gross, C. G. (1998). Spatial maps for the control of movement. *Current Opinion In Neurobiology, 8,* 195-201.

Halgren, E., Dale, A. M., Sereno, M. I., Tootell, R. B., Marinkovic, K., & Rosen, B. R. (1999). Location of human face-selective cortex with respect to retinotopic areas. *Human Brain Mapping, 7,* 29-37.

Hamm, A. O., Weike, A. I., Schupp, H. T., Treig, T., Dressel, A., & Kessler, C. (2003). Affective blindsight: intact fear conditioning to a visual cue in a cortically blind patient. *Brain, 126,* 267-275.

Hasselmo, M. E., Rolls, E. T., & Baylis, G. C. (1989). The role of expression and identity in the face-selective responses of neurons in the temporal visual cortex of the monkey. *Behavioural Brain Research, 32,* 203-218.

Haxby, J. V., Grady, C. L., Horwitz, B., Ungerleider, L. G., Mishkin, M., Carson, R. E. et al. (1991). Dissociation of Object and Spatial Visual Processing Pathways in Human Extrastriate Cortex. *Proceedings of the National Academy of Sciences of the United States of America, 88,* 1621-1625.

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2000). The distributed human neural system for face perception. *Trends in Cognitive Sciences, 4,* 223-233.

Haxby, J. V., Hoffman, E. A., & Gobbini, M. I. (2002). Human neural systems for face recognition and social communication. *Biological Psychiatry, 51,* 59-67.

Haxby, J. V., Ungerleider, L. G., Clark, V. P., Schouten, J. L., Hoffman, E. A., & Martin, A. (1999). The effect of face inversion on activity in human neural systems for face and object perception. *Neuron, 22,* 189-199.

Hendry, S. H. & Reid, R. C. (2000). The koniocellular pathway in primate vision. *Annual Review of Neuroscience, 23,* 127-153.

Hyvarinen, J. (1981). Regional distribution of functions in parietal association area 7 of the monkey. *Brain Research, 206,* 287-303.

Hyvarinen, J. & Poranen, A. (1974). Function of the parietal associative area 7 as revealed from cellular discharges in alert monkeys. *Brain, 97,* 673-692.

Irvin, G. E., Casagrande, V. A., & Norton, T. T. (1993). Center/surround relationships of magnocellular, parvocellular, and koniocellular relay cells in primate lateral geniculate nucleus. *Visual Neuroscience, 10,* 363-373.

Jackson, G. M., Shepherd, T., Mueller, S. C., Husain, M., & Jackson, S. R. (2006). Dorsal simultanagnosia: An impairment of visual processing or visual awareness? *Cortex, 42,* 740-749.

Kanwisher, N. (2004). The ventral visual object pathway in humans: evidence from fMRI. In L.M.Chalupa & J. S. Werner (Eds.), *The Visual Neurosciences* (pp. 1179-1189).

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

Kaplan, E. (2004). The M, P, and K pathways of the primate visual system. In L.M.Chalupa & J. S. Werner (Eds.), *The Visual Neurosciences* (pp. 481-493). Cambridge (MA): MIT Press.

Kerkhoff, G., Munssinger, U., & Meier, E. K. (1994). Neurovisual rehabilitation in cerebral blindness. *Archives of Neurology, 51,* 474-481.

Kingstone, A., Tipper, C., Ristic, J., & Ngan, E. (2004). The eyes have it!: an fMRI investigation. *Brain and Cognition, 55,* 269-271.

Kleinschmidt, A. & Cohen, L. (2006). The neural bases of prosopagnosia and pure alexia: recent insights from functional neuroimaging. *Current Opinion In Neurology, 19,* 386-391.

Kolb, B. & Taylor, L. (1981). Affective behavior in patients with localized cortical excisions: role of lesion site and side. *Science, 214,* 89-91.

LaBar, K. S., LeDoux, J. E., Spencer, D. D., & Phelps, E. A. (1995). Impaired fear conditioning following unilateral temporal lobectomy in humans. *Journal of Neuroscience, 15,* 6846-6855.

LeDoux, J. E. (1995). Emotion: clues from the brain. *Annual Review of Psychology, 46,* 209-235.

LeDoux, J. E. (1996). *The Emotional Brain*. New York: Touchstone.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience, 23,* 155-184.

LeDoux, J. E. (2002). *Synaptic Self*. New York: Viking.

Livingstone, M. & Hubel, D. (1988). Segregation of form, color, movement, and depth: anatomy, physiology, and perception. *Science, 240,* 740-749.

Maher, L. M., Clayton, M. C., Barrett, A. M., Schober-Peterson, D., & Gonzalez Rothi, L. J. (1998). Rehabilitation of a case of pure alexia: exploiting residual abilities. *Journal of the International Neuropsychological Society, 4,* 636-647.

Mattingley, J. B., Driver, J., Beschin, N., & Robertson, I. H. (1997). Attentional competition between modalities: extinction between touch and vision after right hemisphere damage. *Neuropsychologia, 35,* 867-880.

McCandliss, B. D., Cohen, L., & Dehaene, S. (2003). The visual word form area: expertise for reading in the fusiform gyrus. *Trends in Cognitive Sciences, 7,* 293-299.

McCarthy, G., Puce, A., Gore, J. C., & Allison, T. (1997). Face-specific processing in the human fusiform gyrus. *Journal of Cognitive Neuroscience, 9,* 605-610.

Mcneil, J. E. & Warrington, E. K. (1993). Prosopagnosia - A Face-Specific Disorder. *Quarterly Journal of Experimental Psychology Section A-Human Experimental Psychology, 46,* 1-10.

Mishkin, M., Ungerleider, L. G., & Macko, K. A. (1983). Object Vision and Spatial Vision - 2 Cortical Pathways. *Trends in Neurosciences, 6,* 414-417.

Morris, J. S., DeGelder, B., Weiskrantz, L., & Dolan, R. J. (2001). Differential extrageniculostriate and amygdala responses to presentation of emotional faces in a cortically blind field. *Brain, 124,* 1241-1252.

Pegna, A. J., Khateb, A., Lazeyras, F., & Seghier, M. L. (2005). Discriminating emotional faces without primary visual cortices involves the right amygdala. *Nature Neuroscience, 8,* 24-25.

Perenin, M. T. & Vighetto, A. (1988). Optic ataxia: a specific disruption in visuomotor mechanisms. I. Different aspects of the deficit in reaching for objects. *Brain, 111 (Pt 3),* 643-674.

Price, C. J. & Devlin, J. T. (2003). The myth of the visual word form area. *Neuroimage, 19,* 473-481.

Puce, A., Allison, T., Bentin, S., Gore, J. C., & McCarthy, G. (1998). Temporal cortex activation in humans viewing eye and mouth movements. *Journal of Neuroscience, 18,* 2188-2199.

Rizzo, M., Nawrot, M., & Zihl, J. (1995). Motion and Shape Perception in Cerebral Akinetopsia. *Brain, 118,* 1105-1127.

Ro, T., Wallace, R., Hagedorn, J., Farne, A., & Pienkos, E. (2004). Visual enhancing of tactile perception in the posterior parietal cortex. *Journal of Cognitive Neuroscience, 16,* 24-30.

Robbins, R. & McKone, E. (2007). No face-like processing for objects-of-expertise in three behavioural tasks. *Cognition, 103,* 34-79.

Robertson, I. H. & Halligan, P. W. (1999). *Spatial neglect: A clinical handbook for diagnosis and treatment*. Hove, East Sussex: Erlbaum.

Robertson, I. H., Nico, D., & Hood, B. M. (1995). The intention to act improves unilateral left neglect: two demonstrations. *Neuroreport, 7,* 246-248.

Robertson, I. H., Nico, D., & Hood, B. M. (1997). Believing what you feel: using proprioceptive feedback to reduce unilateral neglect. *Neuropsychology., 11,* 53-58.

Rolls, E. T., Critchley, H. D., Browning, A. S., & Inoue, K. (2006). Face-selective and auditory neurons in the primate orbitofrontal cortex. *Experimental Brain Research, 170,* 74-87.

Rorden, C., Heutink, J., Greenfield, E., & Robertson, I. H. (1999). When a rubber hand 'feels' what the real hand cannot. *Neuroreport, 10,* 135-138.

Schenk, T. & Zihl, J. (1997). Visual motion perception after brain damage .1. Deficits in global motion perception. *Neuropsychologia, 35,* 1289-1297.

Schmolck, H. & Squire, L. R. (2001). Impaired perception of facial emotions following bilateral damage to the anterior temporal lobe. *Neuropsychology., 15,* 30-38.

Schweinberger, S. R. & Burton, A. M. (2003). Covert recognition and the neural system for face processing. *Cortex, 39,* 9-30.

Scott, S. K., Young, A. W., Calder, A. W., Hellawell, D. J., Aggleton, J. P., & Johnson, M. (1997). Impaired auditory recognition of fear and anger following bilateral amygdala lesions. *Nature, 385,* 254-257.

Sherman, S. M. & Guillery, R. W. (1996). Functional organization of thalamocortical relays. *Journal of Neurophysiology, 76,* 1367-1395.

Sherman, S. M. & Guillery, R. W. (2002). The role of the thalamus in the flow of information to the cortex. *Philosophical Transactions of the Royal Society of London B: Biological Sciences, 357,* 1695-1708.

Sommer, M. A. & Wurtz, R. H. (2004). The dialogue between cerebral cortex and superior colliculus: implications for saccadic target selection and collorary discharge. In L.M.Chalupa & J. S. Werner (Eds.), *The Visual Neurosciences* (pp. 1466-1484). Cambridge (MA): MIT Press.

Stein, B. E., Magalhaes-Castro, B., & Kruger, L. (1976). Relationship between visual and tactile representations in cat superior colliculus. *Journal of Neurophysiology, 39,* 401-419.

Tarr, M. J. & Gauthier, I. (2000). FFA: a flexible fusiform area for subordinate-level visual processing automatized by expertise. *Nature Neuroscience, 3,* 764-769.

Tranel, D., Damasio, H., & Damasio, A. R. (1995). Double Dissociation Between Overt and Covert Face Recognition. *Journal of Cognitive Neuroscience, 7,* 425-432.

Trauzettel-Klosinski, S. (2002). Reading disorders due to visual field defects: a neuro-ophthalmological view. *Neuro-Ophthalmology, 27,* 79-90.

Trauzettel-Klosinski, S. & Reinhard, J. (1998). The vertical field border in hemianopia and its significance for fixation and reading. *Investigative Ophthalmology and Visual Science, 39,* 2177-2186.

Ungerleider, L. G. & Mishkin, M. (1982). Two cortical visual systems. In D.J.Ingle, M. A. Goodale, & R. J. W. Mansfield (Eds.), *Analysis of Visual Behavior* (pp. 549-586). Cambridge (MA): MIT Press.

Ungerleider, L. G. & Pasternak, T. (2004). Ventral and dorsal processing streams. In L.M.Chalupa & J. S. Werner (Eds.), *The Visual Neurosciences* (pp. 541-562). Cambridge (MA): MIT Press.

Vallar, G. (1993). The anatomical basis of spatial neglect in humans. In I.H.Robertson & J. C. Marshall (Eds.), *Unilateral Neglect: Clinical and Experimental Studies* (Hove, Sussex: Lawrence Erlbaum Associates.

Van Essen, D. C. (2004). Organization of visual areas in macaque and human cerebral cortex. In L.M.Chalupa & J. S. Werner (Eds.), *Th Visual Neurosciences* (pp. 507-521). Cambridge (MA): MIT Press.

Van Essen, D. C., Anderson, C. H., & Felleman, D. J. (1992). Information-Processing in the Primate Visual-System - An Integrated Systems Perspective. *Science, 255,* 419-423.

Vuilleumier, P. & Schwartz, S. (2001a). Beware and be aware: capture of spatial attention by fear-related stimuli in neglect. *Neuroreport, 12,* 1119-1122.

Vuilleumier, P. & Schwartz, S. (2001b). Emotional facial expressions capture attention. *Neurology, 56,* 153-158.

Wang, K., Hoosain, R., Yang, R. M., Meng, Y., & Wang, C. Q. (2003). Impairment of recognition of disgust in Chinese with Huntington's or Wilson's disease. *Neuropsychologia, 41,* 527-537.

Weiskrantz, L. (2004). Blindsight. In L.M.Chalupa & J. S. Werner (Eds.), *The Visual Neurosciences* (pp. 657-669). Cambridge (MA): MIT Press.

Weiskrantz, L., Warrington, E. K., Sanders, M. D., & Marshall, J. (1974). Visual capacity in the hemianopic field following a restricted occipital ablation. *Brain, 97,* 709-728.

Xu, X., Ichida, J. M., Allison, J. D., Boyd, J. D., Bonds, A. B., & Casagrande, V. A. (2001). A comparison of koniocellular, magnocellular and parvocellular receptive field properties in the lateral geniculate nucleus of the owl monkey (Aotus trivirgatus). *Journal of Physiology, 531,* 203-218.

Young, A. W., Hellawell, D., & De Haan, E. H. F. (1988). Cross-Domain Semantic Priming in Normal Subjects and A Prosopagnosic Patient. *Quarterly Journal of Experimental Psychology Section A-Human Experimental Psychology, 40,* 561-580.

Zald, D. H. (2003). The human amygdala and the emotional evaluation of sensory stimuli. *Brain Research Reviews, 41,* 88-123.

Zeki, S. (1991). Cerebral akinetopsia (visual motion blindness). A review. *Brain, 114 (Pt 2),* 811-824.

Zihl, J., von Cramon, D., & Mai, N. (1983). Selective disturbance of movement vision after bilateral brain damage. *Brain, 106 (Pt 2),* 313-340.

Section 2

Reviews

Chapter 3

The effect of visual training for patients with visual field defects due to brain damage. A systematic review

Lies Bouwmeester, Joost Heutink & Cees Lucas
Journal of Neurology, Neurosurgery and Psychiatry (2007); 78, 555-564

Abstract

The objective of this review was to evaluate whether systematic visual training leads to (1) a restitution of the visual field (restoration), (2) an increase in the visual search field size or an improvement in scanning strategies (compensation) and (3) a transfer of training-related improvements in activities of daily living such as reading. To retrieve relevant publications, computer-aided searches of databases (Medline, Embase, Cinahl, Cochrane Central Registers of Controlled Trials) and extensive reference tracing and hand searching were performed. Subsequently, all retrieved and blinded studies were scored on methodological quality. 14 studies were included, 2 randomized controlled trials (RCTs) and 12 within-subject repeated measures designs (RMD).

One of the two RCT studies had good quality. The internal validity of the RMD studies varied from poor to good. Five studies reported a significant effect of the vision restoration therapy (VRT), whereas two studies reported no effect using scanning laser ophthalmoscopy or Goldmann perimetry as outcome measure. All authors of the studies on scanning compensatory therapy (SCT) found a significant effect of up to 30° visual search field, a significant increase in reading speed or decrease in reading errors. It is unclear to what extent patients benefit from restoration therapy in relation to a more efficient scanning strategy which enables them to read faster or to avoid obstacles in a better way. No study has given a satisfactory answer. SCT seems to provide a more successful rehabilitation with more simple and user-friendly training techniques. Validated questionnaires provide the most reliable subjective data to assess the transfer of the relevance of training procedures to activities of daily living of the patient. Hence, SCT is recommended until the effect of the VRT is defined.

3.1 Introduction

The largest group of visual disorders after acquired brain injury are homonymous visual field defects (HVFDs). Homonymous hemianopia refers to a loss of perception over half the field of vision, affecting both eyes, due to a deficient cortical representation of parts of the visual field or deficient transmission of information from the chiasm towards the visual cortex. Approximately 20–30% of all patients with cerebrovascular infarction requiring treatment in a rehabilitation centre have HVFDs (Kerkhoff et al., 1994). Some 70% of patients with HVFDs show a spatially disorganized visual search strategy (Zihl, 1995b). Such patients have particular difficulties with reading and visual exploration, which have far-reaching, disabling repercussions on their domestic and vocational lives. These percentages indicate the impact of the HVFDs, and how important structured rehabilitation efforts for this group of patients can be.

Since the beginning of the 20th century, efforts have been made to train patients with homonymous hemianopia systematically (Poppelreuter, 1917). Over the past decades, many authors have found evidence that patients may successfully adapt to their HVFDs by training. Some authors claim that their rehabilitation methods lead to restitution of part of the HVFDs (Julkunen et al., 2003; Kasten et al., 2000; Kasten et al., 2001; Kasten & Sabel, 1995; Sabel et al., 2004). According to this view, training reactivates surviving neurons of the partially damaged brain structure itself - that is, the border region (transition zone) or islands of residual vision that exist in some patients with cortical damage. This is also called border shift (Kasten et al., 2000). Other authors have found evidence that patients may successfully adapt to their HVFDs by compensatory oculomotor strategies - that is, by learning to make large eye movements into the blind hemifield, thereby enlarging the field of search and improving visually guided activities of daily living (Kerkhoff et al., 1992b; Kerkhoff et al., 1994; Nelles et al., 2001; Pambakian et al., 2004; Zihl, 1995b).

Recently, Pambakian et al. (2004) found that patients with lesions <6 months old with HVFDs adapt themselves to the loss of HVFDs (e.g. by orienting) in the absence of training. This does not tend to occur in the presence of unilateral spatial neglect. It is not yet clear whether and, if so, which of these two methods is more effective. Neither is it clear whether the patients benefit from both methods in activities of daily living. There is a debate among authors about what instruments

might most accurately measure increase in visual field (Balliet et al., 1985; Reinhard et al., 2005; Sabel et al., 2004; Sabel & Trauzettel-Klosinski, 2005). Despite many years of research, there is no consensus on how to determine a border shift. In general, the compensatory strategy method is accepted, but there is criticism about its effect due to a lack of controlled studies.

Hence, a systematic review was conducted of all relevant studies in order to evaluate the effects of visual training for patients with HVFDs. The three main objectives were to review whether systematic visual training can lead to (1) a restitution of the visual field (restoration), (2) an increase in the visual search field size or an improvement of scanning strategies (compensation) and (3) a transfer of training-related improvements in activities of daily living such as reading.

3.2 Methods

3.2.1 Literature search

Relevant publications were identified by means of computerized searches and citation tracking (Box 3.1). The search strategy included Medline (Winspirs), Embase (Winspirs), Cinahl (Winspirs) and the Cochrane Central Registers of Controlled Trials for the period 1966–2005/07. Furthermore, references of conference reports, references of most relevant studies, citations of most relevant studies and related articles were checked for relevant materials. Vocational reintegration was not included in the search because this term did not provide any useful hits.

3.2.2 Study selection

Studies were selected if they met the following entry criteria: (1) inclusion of only patients with HVFDs due to postchiasmatic lesions of the visual system after brain injury, documented by CT/MRI scans, and patients with left or right field defects ranging from homonymous quadrantanopia to complete homonymous hemianopia, with and without macular sparing; (2) applying the intervention of vision restoration therapy (VRT) or of compensatory saccadic eye movements and visual search strategies - that is, scanning compensatory therapy (SCT); (3) using the outcome measures of visual field size, visual search field, reading time and reading error, and

Box 3.1. Search strategy used for computerized searches identifying the design of randomized controlled trials, of controlled clinical trials, of retrospective studies or of repeated measures design studies

- 1 "Hemianopia"/all subheadings
- 2 Homonymous hemianop*
- 3 Hemineglect
- 4 Hemianopic dyslexia
- 5 Hemianopic alexia
- 6 Hemianopic reading
- 7 Cerebral blindness
- 8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
- 9 Rehabilitation AND hemianop*
- 10 Treatment and hemianop*
- 11 Visual training
- 12 Vision restoration therapy
- 13 "Saccades"/all subheadings
- 14 Eye movement and hemianop*
- 15 Oculomotor rehabilitation
- 16 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
- 17 #8 AND #16
- 18 Activity of daily living
- 19 #17 AND #18
- 21 Quality of life
- 22 #17 AND #21

subjective measures of questionnaires; (4) using the design of RCT, of controlled clinical trial (CCT), of retrospective studies or of RMD studies; (5) using only publications written in English, German or Dutch. The assessment of studies potentially eligible for meeting the entry criteria was done independently by two of the authors (LB and JH). Disagreements were solved by discussion. If disagreement persisted, the judgement of a third reviewer (CL) was decisive. Inter-rater agreement was expressed using Cohen's κ.

3.2.3 Assessment of methodological quality of the trials

It is known that patients with visual deficits due to acquired brain damage are not a homogeneous group (Kerkhoff et al., 1994; Pambakian et al., 2004). Because of the heterogeneity of underlying brain lesions, it is difficult to ensure that control and experimental groups are comparable (Kerkhoff et al., 1994). RCTs are therefore

Box 3.2. Criteria list for assessing the methodological quality of repeated measures design studies

1. Was a representative sample of participants used?
2. Was the size of visual field defect sufficiently specified?
3. Was macular sparing/splitting specified in terms of measurement of macular sparing/splitting?
4. Was restitution of visual field adequately measured?
5. Was visual search field adequately measured?
6. Was reading performance adequately measured?
7. Was functional outcome adequately measured?
8. Were stimuli of outcome measures derived from the stimuli of the training programme or vice versa?
9. Was comorbidity identified as a confounding factor and controlled for?
10. Was spontaneous recovery identified as a confounding factor and controlled for?
11. Were examiners blinded to clinical information from participants?

scarce, and hence RMD studies were included, in which patients act as their own controls. All studies were scored on methodological quality. Two authors (LB and JH) independently assessed the publications with the Cochrane checklist for RCT and with the developed checklist for RMD studies (see supplementary appendix 1). Thirteen criteria were used to evaluate the internal validity and clinical relevance of RCTs. Each criterion was scored as good, moderate or poor. A validated list of criteria for assessing the methodological quality of the RMD studies was not available, hence a list of 11 criteria was developed for assessing study quality (Box 3.2).

Criteria were designed to tap domains of external validity (items 1–3) and internal validity (items 4–11). Three of the criteria described the external validity. The period of time after onset lesion, location of the lesion and aetiology of the lesion were considered important factors for external validity of the studies. Scores on items 4–11 were assumed to be of decisive importance for internal validity. Criteria were designed to tap domains of external validity (items 1–3) and internal validity (items 4–11). Three of the criteria described the external validity. The period of time after onset lesion, location of the lesion and aetiology of the lesion were considered important factors for external validity of the studies. Scores on items 4–11 were assumed to be of decisive importance for internal validity. Four outcome measures were included: size of visual field, size of visual search field (the term visual search field is defined as the area that a patient can actively scan by eye movements but without head movement), reading performance and subjective measures (items 4–7). Fixation control was defined as the criterion to assess whether the restitution of visual field was adequately measured. The aim of the VRT is to increase visual field size by

shifting the absolute visual field border and improving detection ability in areas of residual vision. Stimulation in this area could provoke saccadic eye movements towards the stimulus, which can be misinterpreted as a visual field recovery (Sabel & Trauzettel-Klosinski, 2005). Four confounding factors which could cause bias in the studies were analysed: stimuli of outcome measures derived from stimuli of the training programme or vice versa, comorbidities such as unilateral spatial neglect, period of time after lesion onset and blinding of examiners (item 8–11). Items were scored as good, moderate or poor. Items were equally weighted.

Disagreements with respect to methodological quality were identified and resolved in a consensus discussion. If consensus could not be reached, the third reviewer (CL) made the final decision. The final quality score for each study was based on full consensus between the reviewers.

3.2.4 Data extraction and data analysis

From the original studies, we extracted data on participants (number, gender, age, time after onset, specification of visual field defect, aetiology and location of lesion), pathology from MRI/CT, confounding factors (comorbidity and spontaneous recovery), intervention (visual restoration therapy, compensation visual search therapy), outcome measures and transfer of treatment gains to functional outcome measures. The studies may not be sufficiently similar with respect to outcome measures to allow summarising data statistically. Hence, these studies are described here.

3.3 Results

3.3.1 Literature search and study selection

The systematic literature search yielded 315 publications. Of these, 26 possible relevant studies were retrieved as full articles. As the review deals with a broad question, a sensitive search was performed in order not to miss possibly relevant studies. Consequently, 289 of the 315 publications did not meet the inclusion criteria. Of the 289 papers that were rejected, one third, for example, did not have the proper design as they were case studies. Furthermore, in the majority of the publications, hemianopia was only mentioned in the abstract or keywords as a sign of a particular

disorder, and treatment was, as such, not the focus. This information could in all cases be retrieved from the abstracts.

Assessment of these studies with regard to their potential eligibility for meeting the entry criteria reduced the number of studies to 12. Reference tracing and hand searching yielded four more possibly relevant articles. In total, 14 studies were selected, of which 2 were RCT and 12 were RMD studies. There were 15 disagreements between reviewers on selection of the studies and extraction data, resulting in a moderate interreviewer agreement Cohen's κ of 0.54. All disagreements were resolved by discussion; consequently, there was no need to consult the third reviewer for a final decision.

Two RCT studies (Kasten et al., 2000; Kasten et al., 2001) and five RMD studies (Balliet et al., 1985; Julkunen et al., 2003; Kasten & Sabel, 1995; Reinhard et al., 2005; Sabel et al., 2004) described the effect of VRT. Seven studies with RMD (Kerkhoff et al., 1992a; Kerkhoff et al., 1992b; Kerkhoff et al., 1994; Nelles et al., 2001; Pambakian et al., 2004; Zihl, 1995a; Zihl, 1995b) described the effect of SCT, of which two were focused on reading problems. A total of 420 patients who fulfilled the abovementioned inclusion criteria were taken into account for this study. In all, 70 out of 420 subjects participated in the RCT (34 in the experimental group and 36 in the control group) and 350 in RMD studies; 64 patients were trained using the VRT and 286 patients using the SCT.

3.3.2 Assessment of methodological quality of the trials

Table 3.1 gives a detailed description of the included studies. The studies are listed according to the type of training and year of publication.

The agreement of the methodological quality assessment of the two authors (LB and JH) was high and after discussion full consensus was reached. Methodological quality scores of included studies are presented in Table 3.2.

Table 3.1. Characteristics of included studies

Study	Method	Participants	Intervention	Outcome measures	Effect	Remarks
Vision restoration therapy						
Reinhard *et al* (2005).	RMD study rm: 2 Before training After training (No follow-up)	17 patients tao > 1 year lesion location: in central visual pathways Mean age: 49 (range 24-72)	VRT: Nova Vision, 6 days a week, 60 min sessions, length of intervention: 6 months. Fixation control: no Head and eye movements: no	Objective: SLO difference of ratio before after training = E., 0.14E = 1 degree. ADL: text presented in the SLO, reading speed, wpm Subjective: Reports of patients	Objective: SLO: no increase bordershift ADL: reading speed: 6% improvement: not relevant Subjective: 2/3 satisfied with training; 6 satisfied with reading; 4 not satisfied, 4 no reading problem before training	Pathology heterogeneous Outcome not comparable with other studies, no comparison between SLO and HRP/TAP No correlation of objective results with subjective reports, no clear data Good internal validity
Sabel *et al* (2004)	RMD study rm: 2 Before training After training (No follow-up)	16 patients, post hoc 2 groups, COM (n = 9) and INC (n = 7), tao: > 1 year lesion location: post-chiasmatic. Mean age: 49.3 (range 24-72)	VRT: Nova Vision, 6 days, twice a week, 30 min sessions, length of intervention: 6 month. Fixation control: no Head and eye movements: no	Objective SLO difference of ratio before after training = E., 0.14E = 1 degree, HRP, number of hits, TAP, number of misses Subjective: Standardized vision state questionnaire Vision change questionnaire Reports of patients	Objective: SLO: no increase border shift HRP: 5.28°- 7.01° (± 0.20°) increase in border shift HRP and TAP: OD 4.56°- 6.05° (0.20°); OS 4.49°- 5.47° (0.21°) increase in border shift Subjective: 87.5 % satisfied with VRT Vision state questionnaire: 10% improvement Vision change questionnaire: 14/15 patients improved	Pathology heterogeneous Efficacy of VRT depends on which outcome measure is used Subjective: Reading: no clear data No relationship between improvement in perimetric procedures and subjective vision Good internal validity
Julkunen *et al* (2003)	RMD study rm : 3 Before training After training After follow up Follow-up period: 3 months	5 patients tao >1 year lesion location: 1 left occipital inf 1 left occipital ich 1 right temporal ich 1 left multiple ich 1 right tempero-occipital inf extending to thalamus : Age: 18-70	VRT: developed computer program training, 3 times a week, 60 min sessions, length of intervention: 33-47 h (3-4 months) Fixation control: yes Head and eye movements: no	Objective: Kinetic: Goldmann, degrees Static: Octopus101, degrees VEP, latency in ms Subjective: questionnaire	Objective: Perimetry: yes VEP: yes, Subjective: improvement 2 decline 2 no change 1	Pathology: homogeneous Detailed description of patients No clear data of objective outcome measures and subjective data of reading No general conclusions due to small group Moderate internal validity

Table 3.1. Characteristics of included studies (cont)

Study	Method	Participants	Intervention	Outcome measures	Effect	Remarks
Vision restoration therapy (cont)						
Kasten *et al* (2001)	Randomized trial double blind Follow-up study RCT 1998 Follow-up period: mean (SD) 23.5 (2.3) months	22 patients, exp.group (n=16) plac. group (n=6) tao >1 year lesion location: post-chiasmatic - optic nerve. Mean age exp.group 47,7 (12.9), plac. group 55.3 (range 16.2)	VRT: exp. group: Visure, Seetrain, plac.group: Fixtra, daily, 60 min sessions, length of intervention: 150 h within 6 months Fixation control: yes Head and eye movements: no	Objective: PeriMa, number of stimuli PeriForm, number of forms PeriColor,number of colours TAP, number of hits and misses Subjective: Questionnaire	Objective: Mean (SD) exp.group increase 0.4° (0.9°), plac. group increase 0.13° (0.6°) Subjective: From study 1998	Pathology : heterogeneous Different outcome measures and VRT in comparison with pre- and post treatment period (Kasten, 1998), hence incomparable with data of before- and after training No blinding of participants No subjective data from this study Poor internal validity
Kasten *et al* (1998)	Two randomized controlled trials 1. optic nerve 2. postchiasmatic included : postchiasmatic trial (No follow-up)	46 patients, Exp.group (n=18) plac. group (n=30) tao >1 year lesion location: post-chiasmatic and optic nerve Mean (SD) age exp.group 47,7 (12.9), plac. group 55.3 (16.2)	VRT exp. group: Nova Vision Plac. group: fixation training program, daily, 60 min sessions, length of intervention: 6 months. Fixation control; no Head and eye movements: no	Objective: Primary: HRP, Secondary: TAP Subjective: Pre-trial: history interview Post-trial: questionnaire	Objective: Primary: improvement exp. HRP: 29.4% bordershift 4.9° (1.7), placebo HRP: 7.7% Border shift -0.9° (0.8) Secondary: improvement exp. TAP border shift 0.43 ° (0.34) placebo TAP -0.51 ° (0.34) Subjective improvements: Exp. 72.2%, placebo: 16.6%	Pathology: heterogeneous Subjective measures: no separate outcome measures optic nerve lesion and postchiasmatic Good internal validity
Kasten *et al* (1995)	RMD study rm : 2 Before training After training No follow-up	14 patients tao: 0.5-240 months lesion location: post-chiasmatic. Mean age 48.5	VRT Visure, Seetrain, Formtrain, daily, 60 min sessions, length of intervention 80-300 h Fixation control: no Head and eye movements: no	Objective: Static perimetry: Perimat, Periform, Pericolor: Dynamic: TAP Subjective: None	Objective: Improvement: Perimat : 41.6% in 9 of 11 patients Periform: 37.4% , depending on hours of training Pericolor: 25.7 % TAP: unclear	Pathology heterogeneous Specific training effect light, form and colour: modality specific Within first 20 hours no training effect, increase effect from 30 hours Moderate to poor internal validity

Table 3.1. Characteristics of included studies (cont)

Study	Method	Participants	Intervention	Outcome measures	Effect	Remarks
Vision restoration therapy (cont)						
Balliet *et al* (1985)	RMD study rm : 2 Before training After training (No follow-up)	12 patients tao: 5 -36 months, lesion location: occipital Age: 56-66	VRT Goldmann perimeter, compensation training for patients who failed VRT: Goldmann, 2-5 days a week, 60 min sessions, length of intervention : 2-11 months Fixation control: yes Head and eye movements: no	Objective: Goldmann perimeter Subjective: Reports of patients	Objective: Restitution: Goldmann perimeter: 1° Compensation: 0° Subjective: Report of patients: no changes in visual field	Pathology homogeneous Used same instrument for test and training (Goldmann), bias on training effect Emphasis on discussing measurement error caused by compensation eccentric fixation and on good fixation control Moderate to poor internal validity
Scanning compensatory therapy						
Pamba-kian *et al* (2004)	RMD study rm: 4 2 Before training 2 After training Follow-up: 1 month	31 patients, tao: 3 to >12 months lesion location: postchiasmatic Mean age: 49.7 (range 24-75)	Compensation training: developed home training on a monitor, daily, 40 min sessions length of intervention: 1 month	Objective: Humphrey Response time, error rates ADL: response time Subjective: Standardized questionnaire Kerkhoff	Objective: Restitution: 0° Compensation:76% improvement ADL: 31 patients 25% improvement Subjective: Improvement of 27 patients S ($p < 0.001$)	Pathology: heterogeneous Used same instrument for test and training, bias on training effect Controlled for age: elderly patients benefited more from training Moderate internal validity
Nelles *et al* (2001)	RMD study rm: 2 Before training After training Follow-up: 8 months from 15 patients	21 patients, mean tao: 1.5 months (range 0.5-24), no description of lesion location Mean age: 59.2 (3.5) Subgroups: A: eyes fixating B: exploratory eye movements	VRT and compensation training on a board (CVFT), daily, two 30 min sessions length of intervention: 1 month	Objective: TAP CVFT Reponse time, error rates Subjective: Standardized questionnaire Kerkhoff with item reading added	Objective: Restitution: not mentioned Compensation: improvement group A: NS group B: S ($p \leq 0.02$) Subjective: improvement S ($p = \leq 0.05$)	Pathology: no description Outcome measure and intervention are alike: bias on training effect Follow-up effect: no outcome measures Poor internal validity

Table 3.1. Characteristics of included studies (cont)

Study	Method	Participants	Intervention	Outcome measures	Effect	Remarks
Scanning compensatory therapy (cont)						
Zihl (1995)	RMD study rm: 2 Before training After training (No follow-up)	14 patients, mean tao: 11 weeks (range 6-18) lesion location: striate cortex, thalamus, occipito-parietal Mean age: 44 (range 23-74)	Compensation training: saccadic eye movements with TAP, searching task with slides, 30 min sessions length of intervention: 16 (range 8-23) .	Objective: TAP Visual scanning: Pupil-corneal-reflection method, search time, length of scanpath, number of fixations Subjective: Complaints before and after training	Objective: Restorative: no Visual scanning: improvement three variables S ($p < 0.0001$) Subjective: Reduction of complaints	Pathology: homogeneous Emphasis of study on oculomotor scanning After damage in occipito-parietal cortex, optic radioation, striate cortex more training sessions necessary than after occipital lesions No clear subjective measures Moderate internal validity
Kerkhoff *et al* (1994)	RMD study rm: 3 Before training After training After follow up Follow-up period: mean 3 months (1-12)	22 patients, mean tao: 7.5 months (range 1-37), lesion location: occipital: 12 occipito-temporal: 3 temporal: 17 Mean age: 46 (range 16-77)	Compensation training: training in 3 steps: large saccades on large screen, visual search with slides, transfer to ADL, 5 days a week, 30 min sessions length of intervention: 1-3 months	Objective: TAP Visual search field: TAP, slides, table test Subjective: Standardized questionnaire Kerkhoff	Objective: Restitution: mean increase 6.6 ° (range 2° -24°) visual search field increase: mean 30° search time decrease: S ($p <$ 0.01), reduction of errors: 50% Subjective: Significant improvements: S ($p <$ 0.01)	Pathology: homogeneous Left vs right hemianopia, early vs late training no significant differences All patients returned to previous job Good internal validity
Kerkhoff *et al* (1992)	RMD study rm: 3 Before training After training After follow up Follow-up period: Mean 22 months	122 patients, VFD group (n= 92), VFD+ group (n=30), included VFD group, mean tao: 32.8 months (range 1-220) lesion location: postchiasmatic. Mean age: 49 (range 17-74)	Compensation training: training in 3 steps: large saccades on large screen, visual search with slides, transfer to ADL 5 days a week, 30 min sessions length intervention: 6 weeks	Objective: TAP Subjective: None	Objective: Restitution: mean increase: 1.6° (range 1° to 30°), Visual search field increase: mean 30°	Pathology: heterogeneous More training sessions necessary during training with head movements. tao, aetiology, type of visual field defect, visual field sparing and age are irrelevant for treatment success Moderate internal validity

Table 3.1. Characteristics of included studies (cont)

Study	Method	Participants	Intervention	Outcome measures	Effect	Remarks
Compensatory therapy focused on reading						
Kerkhoff *et al* (1992)	RMD study rm: 3 Before training After training After follow up Follow-up period: mean 22 months (range 0.5 - 5 years)	56 patients, mean tao: 40.2 weeks (range 3-220), no description of lesion location Mean age: 46.8 (range 13-74)	Compensation training: computer based method with moving text, 5 days a week, 40 min sessions, length of intervention: 14 sessions	Objective: TAP Reading time Reading errors Subjective: Standardized questionnaire Kerkhoff	Objective: Restitution mean increase: 1.6° Reading time reduction: S ($p \leq 0.02$) Reading errors reduction: before treatment: 4.97 (8.1) after follow-up: 1.48(1.66) Subjective data: not reported	Pathology: heterogeneous Most severely disturbed patients benefited most during training Reduction reading time irrespective of initial reading time before training Good internal validity
Zihl (1995)	RMD study rm: 2 Before training After training (No follow-up)	20 patients, LH group (n= 10), RH group (n= 10) Mean (SD) tao: LH 3-12 weeks (5.8), RH 4-9 weeks (5.9), No description of lesion location. Mean age: LH group 39 (range 21-53), RH group 37 (range 19-54)	Compensation training: computer based with moving text, 5 days a week. 40 min sessions Mean length of intervention: LH 11(range 8-16) sessions, RH 22 (range 9-29).	Objective: TAP Pupil-corneal reflection method Reading speed Subjective: none	Objective: Restitution: no Reading speed: LH 76→113 wpm RH 53→96 wpm Perceptual span: LH 3.75°→4.03° RH 2.79°→3.74°	Pathology: heterogeneous Clear relationship between improvements in reading performance and changes of eye movements parameters Moderate to good internal validity

Key to abbreviations:

exp. = experimental
HRP = High-resolution perimetry
ich = intracerebral hemorrhage
inf = infarction
LH = left-sided hemianopia
NS = not significant
min = minutes
OD = right eye
OS = left eye
plac. = placebo
RCT = randomized controlled trial
RH = right-sided hemianopia
rm = repeated measures
RMD = repeated measurements design
S = significant
SLO = scanning laser ophthalmoscope
tao = time after onset
TAP = Tübinger automatic perimeter
VEP = Visual evoked potential
VRT = vision restoration therapy

Table 3.2. Methodological quality scores of included studies of repeated measures design (in alphabetical order on restoration and compensation therapy).

First author (year)	External validity			Internal validity							
	1	2	3	4	5	6	7	8	9	10	11
Vision restoration therapy											
Balliet *et al.* (1985)	G	G	G	M	M	-	P	P	M	M	P
Kasten *et al.* (1995)	M	G	M	M	-	-	P	M	P	M	P
Julkunen *et al.* (2003)	G	M	P	M	-	-	M	G	M	G	P
Sabel *et al.* (2004)	G	M	M	G	-	-	G	G	M	G	P
Reinhard *et al.* (2005)	G	M	M	G	-	P	P	G	M	G	P
Compensatory therapy											
Kerkhoff *et al.* (1992)	G	M	P	M	M	-	P	G	G	M	P
Kerkhoff *et al.* (1994)	G	M	P	M	G	-	G	G	G	M	P
Zihl (1995)	G	G	M	M	M	-	M	G	M	M	P
Nelles *et al.* (2001)	G	M	P	-	M	-	G	P	P	P	P
Pambakian *et al.* (2004)	G	M	P	M	G	-	G	M	M	M	P
Compensatory therapy focused on reading											
Kerkhoff *et al.* (1992)	G	M	G	M	-	G	P	G	G	M	P
Zihl (1995)	G	G	G	-	-	M	P	G	G	M	P

Numbers correspond to questions in checklist for assessing methodological quality of studies with within-subject repeated measures design (see appendix).

Note: G: good, M: moderate, P: poor

Of the studies that reported the effect of VRT, the RCT of Kasten et al. (2000) had good internal and external validity, but the follow-up study of Kasten et al. (2001) had poor internal validity. Of the RMD studies that reported the effect of the VRT, the studies of Sabel et al. (2004) and Reinhard et al. (2005) had good internal validity. The study of Julkunen et al. (2003) had moderate internal validity. Two studies (Balliet et al., 1985; Kasten & Sabel, 1995) had moderate to poor internal validity. Both studies were included in this systematic review because they contributed to the development of the rehabilitation of the patients with homonymous hemianopia. Balliet (1985) was the first author to discuss the issue of an adequate fixation control, but did not have access to the developed instrumental measurements of the later studies. The study of Kasten & Sabel (1995) was an open pilot trial, which was followed in 1998 by the RCT study (Kasten et al., 2000). Five studies (Julkunen et al., 2003; Kasten et al., 2000; Kasten et al., 2001; Kasten & Sabel, 1995; Sabel et al., 2004) reported a significant effect of VRT, whereas two studies (Balliet et al., 1985; Reinhard et al., 2005) reported no effect of VRT.

Of the studies focused on SCT, the study of Kerkhoff et al. (1992a; 1994) had good internal validity, whereas the study of Zihl (1995a) had moderate to good internal validity; the studies of Zihl (1995b), Pambakian et al. (2004) and Kerkhoff et al. (1992b) had moderate internal validity, and the study of Nelles et al. (2001) had poor internal validity. All authors found a significant effect of up to 30° visual search field, or a significant increase in reading speed or decrease in reading errors.

3.3.3 Data extraction and data analyses

Two RCT publications (Kasten et al., 2000; Kasten et al., 2001) were analysed. The first study (Kasten et al., 2000) describes the pre-treatment and post-treatment effects of restorative therapy, the second study (Kasten et al., 2001) describes the follow-up. The RCT of Kasten et al. (2000) assessed in two independent trials the effect of VRT in patients with optic nerve lesion or postchiasmatic brain injury. This review included only the trial of the post-chiasmatic lesions, which had a good methodological score on randomization, blinding and comparability of the groups. Kasten found a border shift of 4.9° using high resolution perimetry (HRP), but a border shift of 0.43° using Tuebinger automatic perimeter (TAP). In the follow-up study of Kasten et al. (2001), the patients were recruited from the original population of the study of Kasten et al. (2000). This study had poor internal validity, since the

placebo group in the follow-up study was not blinded. All patients treated with placebo had been offered VRT after completion of the previous trial. Also, the number of patients treated with placebo was small.

Out of 10 patients in the placebo group, only 6 were re-examined. Different types of restoration therapy and outcome measures were used in comparison with the pre-treatment and post-treatment periods (Kasten et al., 2000; Kasten et al., 2001). Consequently, the outcome measures of the follow-up period were incomparable with the data before and after training.

3.3.4 Analysis of the RMD publications

All studies gave a good description of the characteristics of the population. Only Kasten et al. (1995) did not mention explicitly the inclusion and exclusion criteria. However, lesion location was specified in only two of the VRT studies (Balliet et al., 1985; Julkunen et al., 2003) and in two of the compensatory therapy studies (Kerkhoff et al., 1994; Zihl, 1995b). All other studies only described the lesions as post-chiasmatic and therefore, in many studies, it remained unclear to what extent the outcome was influenced by comorbidity. Two of the VRT studies (Balliet et al., 1985; Kasten & Sabel, 1995) and two of the compensatory therapy studies (Zihl, 1995a; Zihl, 1995b) scored good on defining the size of the visual field defect. All other studies only described left or right, complete or incomplete HVFDs, and were therefore rated as moderate. Macular sparing/splitting was not mentioned in the majority of the compensation therapy studies (Kerkhoff et al., 1992b; Kerkhoff et al., 1994; Nelles et al., 2001; Pambakian et al., 2004), whereas in the majority of the VRT studies the macular sparing/splitting was adequately measured.

Of the five VRT studies, restitution of the visual field was adequately measured in two studies (Reinhard et al., 2005; Sabel et al., 2004). The method used in these studies provides a simultaneous assessment of the retinal image and the stimulus in the central 10° visual field, thus allowing an absolute fixation control. Although all authors used the enlargement of the visual field as an outcome measure of the VRT, the instruments determining visual field were very diverse and made an overall effect estimate impossible. Sabel et al. (2004) found no effect on border shift using SLO, whereas he found an absolute border shift of 1.73° using HRP. Reinhard et al.'s study (2005) used SLO and found no change in the absolute field defect border after training. Julkunen (2003) used two perimetric methods and is the only author

who applied pattern reversal visual evoked potential as an outcome measure. After training, there was a significant change of 5° in visual angle using the dynamic Goldmann perimeter and static Octopus101 perimeter. In 9 of the 11 patients Kasten & Sabel (1995) found a visual field enlargement using the Perimat test, with an average of 41.6%, and did not mention data regarding border shift of the visual field. No clear data were found using TAP. Balliet et al. (1985) found <1° of apparent visual field change using the dynamic Goldmann perimeter. In five SCT studies (Kerkhoff et al., 1992a; Kerkhoff et al., 1992b; Kerkhoff et al., 1994; Pambakian et al., 2004; Zihl, 1995b) the measurement of the restoration of visual field was not the focus of the study and was considered a byproduct of the visual training. These studies were defined as moderate. Zihl (1995b) and Pambakian et al. (2004) found no effect. Kerkhoff et al. (1994) found a mean increase of 6.6° (range 2° to 24°), Kerkhoff et al. (1992a) a mean increase of 1.6° (range 1.0° to 20°) and Kerkhoff et al. (1992b) a mean increase of 1.6° (range 1.0° to 30°). The clinical significance of the effect of an intervention depends on how large the treatment effects are in clinical practice. The VRT studies reported an effect of up to 5° increase in visual field size. This small effect could be clinically significant for reading, for fluent reading the visual span has to be extended up to 5°, whereas for scanning scenes this effect is too small to be clinically significant. An effect of up to 40° would be clinically significant enough for the subject to be able to explore the world as reported by the SCT studies.

Among the SCT studies, visual search field was adequately measured in the studies by Kerkhoff et al. (1994) and Pambakian et al. (2004), since different methods for measuring VSF were used. The studies of Zihl (1995b), Nelles et al. (2001) and Kerkhoff et al. (1992b) were judged moderate using only one outcome measure. All studies showed an improvement in scanning strategies of up to 30° in the 46° VSF of the hemianopic visual field. As they used different instruments to measure the VSF, an overall effect estimate was not possible. Among the VRT studies, only the study of Balliet et al. (1985) trained and measured VSF as an effect on restitution. He found very small changes in VSF. The study was judged as moderate.

Kerkhoff et al. (1992a) scored good on the retest reliability of the reading test. Zihl (1995a) used a standardized reading test and his study was judged moderate. In both studies, reading time and reading errors improved significantly. Of the VRT studies, only the study by Reinhard et al. (2005) measured the reading performance as

the effect of VRT training. The study scored poor on the measurement of reading performance. The increase of 6% in reading performance after VRT is hence doubtful. With regard to the subjective measures of improvement, a difference was found between restorative studies and compensatory studies. A total of four studies of compensatory therapy used validated or standardized questionnaires (Kerkhoff et al., 1994; Nelles et al., 2001; Pambakian et al., 2004; Zihl, 1995b). Only one study of restorative therapy (Sabel et al., 2004) used a validated questionnaire.

In the studies by Balliet et al. (1985) and Nelles et al. (2001), most of the stimuli that were used in training were also used in the evaluation of improvement, and therefore this criterion was judged as poor. Only the studies of Kerkhoff et al. (1992a; 1992b; 1994) and Zihl (1995a) described the use of neuropsychological tests to exclude comorbidities such as visuospatial disorders, and visual agnosia and alexia as confounding factors.

Three recent VRT studies controlled for spontaneous recovery and only trained patients who were >1 year post-lesion (Julkunen et al., 2003; Reinhard et al., 2005; Sabel et al., 2004). In none of the RMD studies were the examiners blinded to clinical information from participants.

3.4 Discussion

The methodological quality of the studies ranged from poor to good. Only two RCT studies could be selected from the literature search and therefore RMD studies were included in the search.

However, a repeated measures design implicates less control, and internal validity is by definition lower compared with RCT studies. In order to assure internal validity of the RMD studies, it is necessary to ensure that no factors other than the intervention itself determine the outcome measure. Therefore, quality assessment was performed using a developed criteria list focused on the internal validity and in particular on information bias and confounding factors.

Strikingly, none of the RMD studies reported whether examiners were blinded to clinical information from participants. Hence we cannot exclude the possibility that examiners could have been influenced by the results of the training or by seeing previous perimetry results before each measurement. As a consequence, bias of

outcome measures cannot be excluded. To resolve this issue, blinding of examiners should be pursued in future studies.

Only a few studies controlled for visual neglect and visual agnosia with neuropsychological tests (Kerkhoff et al., 1992a; Kerkhoff et al., 1992b; Kerkhoff et al., 1994; Zihl, 1995a). Most studies did not pay much attention to the possibility of higher visual disorders. In our experience, cases of ‘‘pure’’ hemianopia are relatively rare because in most cases parts of the occipital pole (BA 17) as well as other, more anterior brain regions are damaged. The chances of higher order disorders supplementary to the hemianopia are quite high when the occipitotemporal or occipitoparietal regions are involved. Since in most studies patients were selected on the basis of having post-chiasmatic lesions, it is unlikely that lesions of all these patients were limited to the occipital pole.

The size of the visual field defect and the presence or absence of macular sparing or splitting depends on the location of the brain lesion and varies between patients. In general, macular sparing in hemianopia occurs only when the lesion is limited to the occipital pole. Hence, it should be analysed carefully and expressed in the outcome measures. The majority of the studies did not specify these factors, which might be of importance for the chances of successful rehabilitation. Except for the studies of Kerkhoff et al. (1994) post hoc, Kasten et al. (2001) and Sabel et al. (2004), in none of the studies was the size of the HVFD taken into account as a weighed measure in the analysis of improvement after treatment.

Among the five studies that met the entry criteria of the restoration intervention, a certain line of research can be distinguished starting from the study of Balliet et al. (1985) to the recent study of Reinhard (2005). Zihl and von Cramon were the first to evaluate systematically the effects of specific perimetry training on visual field size in visual field defects (Zihl & von Cramon, 1985). Since the 1980s, there has been considerable development in the quality of methods and instruments to assess visual fields and fixation control. Our review shows no consensus between different authors about which methods should be used to measure the exact size of the visual field and improvements in the transition zone. Some authors (Balliet et al., 1985; Reinhard et al., 2005) claim that studies using perimetric or campimetric methods do not control sufficiently for eye movements or para-central fixation. There is a discussion about a mismatch of border position between SLO on the one hand and HRP/TAP on the other hand. In most patients the SLO is noticeably closer to the

midline than the HRP/TAP border (Sabel et al., 2004). In all studies, the original size of the visual field defect and also the efficacy of VRT depended on the method of the perimetric measurements and on the fixation control that was used. Thus, the apparent visual field defect is greater when measured with SLO than when measured with HRP or TAP. After VRT, the mismatch is even more pronounced. To our knowledge, this matter has not been resolved.

Potential confounders are the effect of practice in detection or discrimination tasks, and measurement errors due to improper fixation, which can cause eccentric fixation. Improper alignment in the baseline measurement can cause a mismatch border position.

It would have been very useful to evaluate whether an improvement in the transition zone also leads to an improvement in the VSF. We found no strong evidence that the possible gain of a few degrees of visual field results in better oculomotor scanning strategies and leads to a better performance of activities of daily living.

If visual search field and relevant activities of daily living such as reading would indeed improve as a result of a small border shift, one would perhaps also expect that the initial size of the VFD before the training would correlate to the level of impairment. To our knowledge, there is no strong evidence that points to this. On the other hand, it seems that in VRT studies there is a basic assumption that patients benifit from reducing the HVFD by a few degrees, which makes it even more necessary to use the size of the initial visual field deficit as a weighed factor in the analysis.

SCT seems to provide a more successful rehabilitation, with more simple and user-friendly training techniques. The data of the studies show that patients performed significantly faster in search strategies after compensatory therapy. Scanning strategies are applied to and trained in real life scenes. However, none of these studies compare the results with those of an untreated control group.

The evidence of the transfer of training-related improvements in activities of daily living of both VRT and SCT is limited. Validated questionnaires seem to provide the most reliable subjective data to assess the translation of the relevance of training procedures to activities of daily living of the patient.

3.5 Conclusion

It is unclear to what extent patients benefit from restoration therapy in relation to a more efficient scanning strategy that enables them to read faster or to avoid obstacles in a better way.

No study has given a satisfactory answer. The discrepancy between the positive results of the restoration by perimetric measurements and the null-SLO finding diminishes the chances of restoration after VRT. The latest discussions prove that restorative therapy requires further study of residual vision.

Transfer of visual search performance in activities of daily living is not sufficiently proven. There is a need for more validated instruments that can measure therapy outcome objectively.

Until the effect of the restoration therapy is further evaluated, visual search therapy is recommended.

Acknowledgements

We thank Professor Dr. J. Zihl for his comments and advise as an expert in the field. We also thank Jos W. Snoek, MD, PhD, neurologist, Anja van de Wege, PhD, Marion Priebe, MSc, and Emiel van Trijffel, MSc, for critically reviewing the draft version of this paper.

References

Balliet, R., Blood, K. M., & Rita, P. (1985). Visual field rehabilitation in the cortically blind? *Journal of Neurology, Neurosurgery and Psychiatry, 48,* 1113-1124.

Julkunen, L., Tenovuo, O., Jaaskelainen, S., & Hamalainen, H. (2003). Rehabilitation of chronic post-stroke visual field defect with computer-assisted training: a clinical and neurophysiological study. *Restorative Neurology and Neuroscience, 21,* 19-28.

Kasten, E., Muller-Oehring, E., & Sabel, B. A. (2001). Stability of visual field enlargements following computer-based restitution training -- results of a follow-up. *Journal of Clinical and Experimental Neuropsychology, 23,* 297-305.

Kasten, E., Poggel, D. A., & Sabel, B. A. (2000). Computer-based training of stimulus detection improves color and simple pattern recognition in the defective field of hemianopic subjects. *Journal of Cognitive Neuroscience, 12,* 1001-1012.

Kasten, E. & Sabel, B. A. (1995). Visual field enlargement after computer training in brain-damaged patients with homonymous deficits : an open pilot trial. *Restorative Neurology and Neuroscience, 8,* 113-127.

Kerkhoff, G., Munssinger, U., Eberle-Strauss, G., & Stogerer, E. (1992a). Rehabilitation of hemianopic alexia in patients with postgeniculate visual field disorders. *Neuropsychological Rehabilitation, 2,* 21-41.

Kerkhoff, G., Munssinger, U., Haaf, E., Eberle-Strauss, G., & Stogerer, E. (1992b). Rehabilitation of Homonymous Scotomas in Patients with Postgeniculate Damage of the Visual-System - Saccadic Compensation Training. *Restorative Neurology and Neuroscience, 4,* 245-254.

Kerkhoff, G., Munssinger, U., & Meier, E. K. (1994). Neurovisual rehabilitation in cerebral blindness. *Archives of Neurology, 51,* 474-481.

Nelles, G., Esser, J., Eckstein, A., Tiede, A., Gerhard, H., & Diener, H. C. (2001). Compensatory visual field training for patients with hemianopia after stroke. *Neuroscience Letters, 306,* 189-192.

Pambakian, A. L., Mannan, S. K., Hodgson, T. L., & Kennard, C. (2004). Saccadic visual search training: a treatment for patients with homonymous hemianopia. *Journal of Neurology, Neurosurgery and Psychiatry, 75,* 1443-1448.

Poppelreuter, W. (1917). *Disturbances of lower and higher visual capacities caused by occipital damage*. Oxford: Clarendon Press.

Reinhard, J., Schreiber, A., Schiefer, U., Kasten, E., Sabel, B. A., Kenkel, S. et al. (2005). Does visual restitution training change absolute homonymous visual field defects? A fundus controlled study. *British Journal of Ophthalmology., 89,* 30-35.

Sabel, B. A., Kenkel, S., & Kasten, E. (2004). Vision restoration therapy (VRT) efficacy as assessed by comparative perimetric analysis and subjective questionnaires. *Restorative Neurology and Neuroscience, 22,* 399-420.

Sabel, B. A. & Trauzettel-Klosinski, S. (2005). Improving vision in a patient with homonymous hemianopia. *Journal of Neuro-Ophthalmology, 25,* 143-149.

Zihl, J. (1995a). Eye movement patterns in hemianopic dyslexia. *Brain, 118 (Pt 4),* 891-912.

Zihl, J. (1995b). Visual scanning behavior in patients with homonymous hemianopia. *Neuropsychologia, 33,* 287-303.

Zihl, J. & von Cramon, C. D. (1985). Visual field recovery from scotoma in patients with postgeniculate damage. A review of 55 cases. *Brain, 108 (Pt 2),* 335-365.

Appendix

Checklist for assessing methodological quality of studies with within-subject repeated measures design

Date: ……..……. Reviewer: ……..
First author: ……. Year of publication: …….
Study title: ……..

External validity

1. Was a representative sample of participants used? good / moderate / poor
2. Was size of visual field defect sufficiently specified? good / moderate / poor
3. Was macular sparing/splitting specified in terms of measurement of macular sparing/splitting? good / moderate / poor

Internal validity

4. Was restitution of visual field adequately measured? good / moderate /poor
5. Was visual search field adequately measured? good / moderate / poor
6. Was reading performance adequately measured? good / moderate / poor
7. Was functional outcome adequately measured? good / moderate / poor
8. Were stimuli of outcome measures derived from the stimuli of the training program or vice versa? good / moderate / poor
9. Was co-morbidity identified as a confounding factor and controlled for? good / moderate / poor
10. Was spontaneous recovery identified as a confounding factor and controlled for? good / moderate / poor
11. Were examiners blinded to clinical information from participants? good / moderate / poor

Item 1 Was a representative sample of participants used?

The following characteristics of the study population were explicitly described:

- inclusion and exclusion criteria, age, sex, time after onset after the lesion, aetiology of the lesion (specified in terms of vascular lesions, trauma, tumour, cerebral inflammation), location of lesion (specified in posterior thalamus, occipito-parietal cortex, temporal cortex, optic radiation, striate cortex) : *good*
- inclusion and exclusion criteria, age, sex, without mentioning time after onset after lesion or without specifying aetiology of the lesion: *moderate*
- not described: *poor*

Specification of the location of the lesion gives the possibility to analyse the influence of other deficits like visuo-spatial disorders or visual agnosia. Time after onset can be an important indication as period of spontaneous recovery. Specification the aetiology of the brain injury is essential since different causes, like a vascular lesion or a tumour can influence the course of the brain injury differently.

Item 2 Was size of HVFDs sufficiently specified?

- specified in degrees and/or diagrams, graphics: *good*
- description left/right, complete/incomplete hemianopia, quadranopia: *moderate*
- not described: *poor*

Item 3 Was macular sparing/splitting specified in terms of measurement of macular sparing/splitting?

- specified in degrees and/or diagrams, graphics: *good*
- description macular splitting/sparing: *moderate*
- not described: *poor*

The size of the HVFDs and the presence or absence of macular sparing/splitting depends of the location of the lesion of the brain and varies between patients. The description of the type of visual field was considered as an important contribution for external validity.

Item 4 Was restitution of visual field adequately measured?

- fixation control was assessed by a method which allowed the investigator to see a display of the retina image, the fixation cross and the stimuli simultaneously: *good*
- fixation control was performed by the patient, for example responding to a randomly change of colour of the fixation point with the control of the investigator and/or of a video camera: *moderate*

- fixation control was performed by the patient for example responding to a randomly change of colour of the fixation point without the control of the investigator and/or by a video camera : *poor*

The aim of the VRT is to increase visual field size by shifting the absolute visual field border and improving detection ability in areas of residual vision. Stimulation in this area could provoke saccadic eye movements towards the stimulus, which can be misinterpreted as a visual field recovery. Therefore fixation control was defined as criterion to assess whether the restitution of visual field was adequately measured.
The following measurement methods are discussed with regard to fixation control:
SLO is a method to detect absolute HVFDs with high spatial resolution. The method provides a simultaneous assessment of the retinal image and the stimulus in the central 10-degree visual field, thus allowing an absolute fixation control.
Perimetric/campimetric instruments are fundamentally different from the SLO.
HRP is a campimetric procedure to detect small visual stimuli above detection threshold and the stimuli are presented in the central 27-degree visual field on a computer monitor. As fixation control the fixation point randomly changes its colour whereupon the patient has to respond. Perimat, Periform and Pericolor are a type of automated perimetry, with various computer programs up to 40 degree visual field. In Perimat small light stimuli are presented in random position on a black screen, Periform examines the patient's ability to recognize orientations and Pericolor assesses colour perception. Fixation was controlled with a video camera.
TAP is a static perimeter where the visual field up to 30 degrees eccentricity is determined by presenting stimuli near threshold detection. The spatial resolution of TAP is relatively low. Fixation is controlled with a video camera. Goldmann is a kinetic perimeter with a visual field up to 180 degrees eccentricity using stimuli in a hemisphere. Fixation is controlled by the investigator.

Item 5 Was visual search field adequately measured?

- combination of tests of visual search field such as perimetric/ campimetric measures, slides, table test: *good*
- only perimetric tests: *moderate*
- no test: *poor*

The term 'visual search field' is defined as the area that a patient can actively scan by eye movements but without head movements. The training of visual search field consists usually of different steps from learning eye movement strategies to systematic scanning strategies. Perimetric tests do not adequately measure scanning strategies. Therefore a combination of tests was defined as a criterion to evaluate if visual search field was adequately measured such as perimetric instruments to assess the visual field and specific visual search field tests as identifying objects visually on a table or on slides.

Item 6 Was reading performance adequately measured?

- retest-reliability of the reading tests was determined : *good*
- standardized reading test were used: *moderate*
- retest-reliability of the reading tests was not determined and no standardized reading tests were used : *poor*

In general reading tests are used for measurement of reading performance, assessing reading time and reading errors. When the tests are highly reliable, they are sensitive to changes in reading performance during therapy. Therefore retest-reliability of the reading tests was defined as criterion to assess whether the reading performance was adequately measured.

Item 7 Was functional outcome adequately measured?

- validated observation of ADL tasks and/or validated questionnaires: *good*
- not validated instruments like structured interviews, questionnaires: *moderate*
- no reported instruments like questions: *poor*

As the functional outcome is a subjective measure, validated questionnaires or validated observations of ADL tasks were defined as criterion to assess functional outcome.

Item 8 Were stimuli of outcome measures derived from the stimuli of the training program or vice versa?

- None of the stimuli of the outcome measures were derived from the stimuli of the training program: *good*
- majority of the stimuli of the outcome measures was not derived from the stimuli of the training program: *moderate*
- majority of the stimuli of the outcome measures was derived from the stimuli of the training program: *poor*

Possible source of bias: using similar stimuli in training programs as in outcome measures.

Item 9 Was co-morbidity identified as a confounding factor and controlled for?

- co-morbidity was mentioned in particular higher order visual deficits like visual neglect, visual agnosia, alexia and neuropsychological tests were performed: *good*
- co-morbidity was only mentioned: *moderate*
- co-morbidity was not mentioned: *poor*

Possible source of bias: higher order visual deficits like visual neglect, visual agnosia, alexia.

Item 10 Was spontaneous recovery identified as a confounding factor and controlled for?

- time of onset was controlled for > 1 year : *good*
- time of onset was controlled for < 1 year and post hoc: *moderate*
- time of onset was not controlled for and only mentioned: *poor*

Possible source of bias: spontaneous recovery since time of onset.

Item 11 Were examiners blinded to clinical information from participants?

- examiners were blinded : *good*
- examiners were not blinded/ not reported*: poor*

To avoid bias it is desirable that examiners proceed without knowing clinical information. Blinding the examiners to clinical information contributes to internal validity.

Chapter 4

Rehabilitation of unilateral neglect

Ian H. Robertson & Joost Heutink
In: W.H.Brouwer, A.H. van Zomeren, I.J. Berg, J.M. Bouma, & E.H.F. de Haan (Eds.)
Neuropsychological rehabilitation: a cognitive approach
Amsterdam: Boom (2002)

4.1 Unilateral spatial neglect

Acquired brain damage to structures of the right hemisphere can lead to the phenomenon of unilateral spatial neglect. Neglect can be characterized as a failure, difficulty or slowness in reporting, interacting with or moving towards objects, sounds or representations as a consequence of their spatial position, most frequently on the left. Although both left and right hemisphere stroke patients are equally likely to suffer from neglect in the acute phase (De Kort, 1996), chronic neglect is almost exclusively caused by right hemisphere lesions (Bisiach & Vallar, 1988; Vallar, 1993). And even though its more florid manifestations usually remit in the very large number of patients who show acute neglect following right hemisphere stroke, it has long-lasting, severe effects on other domains such as motor function (Gialanella & Mattioli, 1992).

The fact that symptoms associated with neglect can be observed in all sensory modalities (i.e. visual, tactile, auditory, olfactory and gustatory) indicates that neglect cannot be explained by a deficit of primary sensory or motor functions, but rather consists of a range of phenomena related to the high level representation of, and attention to, space. Neglect may represent a 'gradient' of attentional bias from left to right, such that there is a continually increasing probability of detecting stimuli the further to the right of external space these stimuli occur. Neglect may not be a unitary disorder. Given that the brain's representation of space is not itself unitary, then it should not be surprising to find that neglect may occur separately for semi-independent spatial areas, each defined with respect to their proximity to the body (Rizzolatti & Berti, 1990; Rizzolatti & Berti, 1993). Three distinct regions of space can be distinguished: personal space (which is delimited by the body itself), peripersonal space (also referred to as reaching space), and extrapersonal space (which is beyond the reach of the arms). Neglect thus, may be a variable and multimodal pattern of dysfunction affecting spatial representation at many different levels in the brain.

What is striking about neglect is the range of brain lesions that appear to be implicated in the disorder (for a recent overview, (Vallar, 2001)). In most literature reviews, neglect is associated with large right hemisphere lesions including the temporoparietal-occiptital junction. Within this region the inferior parietal lobule (IPL) appears to be highly correlated with chronic neglect (Vallar & Perani, 1986).

Some studies, however, indicate that the IPL does not play an exclusive role in chronic neglect. Using neuro-imaging techniques, Samuelsson and co-workers found that neglect was highly associated with middle temporal lobe and/or the temporo-parietal paraventricular white matter (Samuelsson et al., 1997). Karnath et al. showed that for neglect patients without hemianopia (which frequently coincides with neglect), the neuro-anatomical correlate of neglect lies mainly in the superior temporal cortex (Karnath et al., 2001). There is also evidence that unilateral neglect can be caused by a lesion of subcortical regions in the brain such as the thalamus (Watson & Heilman, 1979) and the basal ganglia (Damasio et al., 1980).

These lesion studies suggest that unilateral neglect cannot be linked to a discrete anatomical structure. It is far more likely that neglect is merely the result of a disruption of a large network of anatomically distinct yet functionally connected cortical and subcortical structures which are all (partially) involved in attention and spatial cognition. Apart from neglect, right hemisphere brain damage may also cause non-lateralized (i.e. non-spatial) attentional deficits such as impaired arousal (Heilman et al., 1978) and impaired sustained attention (Robertson et al., 1997a; Wilkins et al., 1987). As we will discuss later on in this chapter, these deficits may also interact with chronic neglect.

4.2 Rehabilitation of Neglect

Unilateral neglect is a particularly appropriate disorder when attempting to develop rehabilitation strategies closely tied to theoretical models derived from cognitive neuroscience. This is in part because of the extensive body of theoretical work that has been devoted to this condition. On the other hand, lesion studies have provided an important basis for models of spatial attention in humans. Finding adequate rehabilitation methods for unilateral neglect is of great importance for at least two reasons. Firstly, neglect is a predictor of poor ADL function even after the most conspicuous symptoms (such as head and eye deviation towards the ipsilateral side and the failure to orient to highly salient stimuli on the contralateral side) have disappeared. Secondly, both temporary and long-term interventions can provide insight into the mechanisms that underlie human spatial attention in general and neglect in particular.

In some cases, it has been shown that neglect can be temporarily or permanently overcome - both in animals and humans. Sprague (Sprague, 1966) for instance demonstrated that a strong spatial bias in cats caused by a large unilateral posterior lesion could be ameliorated by destroying the superior colliculus on the side opposite to initial visual input. There are also examples of this phenomenon in humans: for instance, following a right hemisphere stroke, one patient showed severe left-sided spatial neglect which then disappeared abruptly following a second stroke in the left frontal region (Vuilleumier et al., 1996). A possible interpretation of these data is that the persistence of the neglect was due to inhibition by the intact left hemisphere of the attentional networks in the damaged right hemisphere. When the second lesion in the left hemisphere occurred, this may have reduced the competitive inhibition, thus allowing the impaired attentional circuits in the originally lesioned right hemisphere circuit to function at a more normal level. Whatever the actual underlying mechanism, these data show that *latent* function persisted in the damaged hemisphere but could only be unlocked by an alteration of the dynamic architecture of the brain's attentional or orientational systems. A second lesion to the opposite hemisphere is, however, a rather unethical if not impractical approach to rehabilitation. Nevertheless, these studies show that there is a latent function to be unlocked, and that rehabilitation therapists must strive to find methods to do so. They can only do so by iterative interactions with the models of normal cognitive function that cognitive neuroscience has developed.

4.2.1 Clinically evaluated methods

4.2.1.1 Scanning Training

The only treatment procedure for unilateral neglect to have been submitted to clinical trials with evaluation of long-term effects under controlled conditions consists of scanning training (Antonucci et al., 1995; Weinberg et al., 1977). Scanning training is a behavioural strategy that trains patients to compensate visually for impaired scanning of the neglected left side. It was developed by Weinberg, Diller and colleagues of the Institute of Rehabilitation in New York. Weinberg et al. compared a group that received a standard rehabilitation programme (occupational therapy) with a group that received twenty hours of scanning training over a period of about a month in addition to the standard rehabilitation programme. Scanning training consisted of

several elements, such as a number of modified cancellation tasks, a graded practice in reading and a scanning machine. In the first stages of the reading practice, patients could use a vertical line on the left of the text as an anchoring point in addition to numbers at the beginning and end of each line. These cues were withdrawn as training progressed. First the line numbering on the right was removed, followed by the numbers on the left and ultimately the anchoring line was removed. The scanning machine consisted of a board on which light-stimuli could appear in different positions. Patients were required to track targets that moved from one side of the board towards the other side and to search for lights that appeared in different positions on the board.

Patients who received both conventional training and scanning training benefited significantly compared to the group that received conventional therapy only. The improvements were found mainly on a number of tasks relating to academic performance, such as reading and writing, but did not generalize to tasks such as line bisection or location of the body midline.

However, a large randomized group study by Robertson and colleagues comparing a group that received computer-based scanning training (using techniques similar to those of Weinberg et al.) with a group that received recreational computing, found no significant difference between the two groups (Robertson et al., 1990).

Pizzamiglio and co-workers in the Clinica Santa Lucia in Rome (Pizzamiglio et al., 1992) evaluated the effects of a systematized and extended version of the visual scanning training developed by Diller and Weinberg (1977). Thirteen patients with extensive lesions in the right hemisphere who showed symptoms of both neglect and left visual field deficits due to hemianopia or quadrantopia each received forty sessions of intensive scanning training (five times a week over a period of eight consecutive weeks). Each training session lasted approximately ninety minutes and consisted of four different procedures:

1. Visual scanning training, in which the patients had to detect digits appearing in different sequences on a large screen (2.20 x 1.50 m). The task was to name the digit presented and to press a button as quickly as possible afterwards.
2. Reading and copying training, in which sentences and titles of increasing complexity were presented. In order to encourage complete scanning of the stimuli, a flashing bar was presented on the left side of the paper and the

patients were given both spatial (e.g., “look carefully on your left”) and semantic (e.g., “who has done…?”) cues. As training progressed, the flashing bar and the cues were left out.

3. Copying line drawings on a dot matrix. Patients were presented with a matrix of dots on their left. Some of the dots in the matrix were connected by lines. Patients had to copy these lines in a matrix presented on their right.
4. Figure description, in which patients were shown drawings of simple, realistic scenes. They were cued verbally to describe in detail all elements depicted in the drawings.

In general, patients improved specifically on tasks that required spatial scanning (e.g., letter cancellation), but not on other tasks requiring visuo-spatial functions (e.g., judgment of stimuli orientation). This indicates that although patients were able to apply the learned behavioural strategy to compensate effectively for their deficit in spatial attention in a limited number of tasks, their spatial deficit itself did not change as a result of the training.

In a series of more recent studies, the potential effectiveness of this extremely intensive scanning training combined with optokinetic stimulation was demonstrated by the same group led by Pizzamiglio (Pizzamiglio et al., 1998). Optokinetic stimulation was used to induce a so-called nystagmus reflex in neglect patients. Patients were required to perform a visual scanning task that was presented in the foreground on a large projection screen while the background was moving slowly towards the left thus inducing a slow wave eye-movement from right to left. It is possible that in addition to teaching patients a behavioural strategy to compensate for their spatial deficits, this method also facilitates changes in the attentional system. However, the effects of scanning training on functions such as contralesional motor impairment still remain to be tested.

Though the effectiveness of scanning training in improving visual neglect has been demonstrated, doubts about generalization to other spatial functions were raised by subsequent studies (Gouvier et al., 1987). Indeed, most improvements after scanning training tend to be limited to the same type of task as was used for the training itself.

4.2.1.2 Limb Activation Training

Limb Activation Training (LAT) is a distinctive approach to the rehabilitation of neglect. LAT was developed from a series of experiments based partly on Rizzolatti's premotor model of neglect (Berti & Rizzolatti, 1992; Rizzolatti & Berti, 1993). As mentioned earlier, multiple representations of space can be distinguished in the brain, namely personal, peripersonal and extrapersonal space. According to Rizzolatti, these systems interact to produce a coherent spatial reference system against which purposeful motor movements are calibrated and organized. As the parallel activity of these different perceptuo-motor neural maps produces the normal representation of space, it is the breakdown of one or more of these systems in neglect that creates a distorted representation of space.

In a series of experiments (Robertson & North, 1992; Robertson & North, 1993), a number of conditions were compared to determine the effects of finger movements. In the first condition patients were required to make finger movements with their left hand while performing a visual scanning task. In the second condition patients had to perform the same task but were now required to scan the left side visually the same number of times that they made finger movements in the first condition (i.e. subjects received a general instruction to "find the left arm" prior to each trial). Making finger movements significantly reduced neglect. Visuo-perceptual anchoring did not reduce neglect.

A second comparison was made between movements of the fingers of the left hand that were made 'out of sight', in left and right hemispace. Only left hemispace 'blind' finger movements significantly reduced neglect compared to the standard condition. Thirdly, blind movements of the fingers of the left hand in left hemispace were compared with passive visual cueing (reading a changing number), and again it was found that only the finger movements reduced neglect. Finally, movements of the fingers of the right and left hands in left hemispace were compared. Only the latter reduced neglect. These findings have been replicated in a large group study (Ladavas et al., 1997).

These results suggest that this potent effect of moving the hemiplegic side results from actually making movements with the left limb in left hemispace and is not simply because the result of cueing attention to the neglected side. Interpreting these data in terms of Rizzolatti's model, one could argue that by inducing the subject to make voluntary movements with the left hand in left hemispace, activity in the left

half of the somatosensory personal space was activated or enhanced. The integrated nature of the somatosensory and peripersonal spatial systems resulted in enhanced activation of the impaired half of peripersonal space. But why did left-hand movements in right hemispace not similarly activate the left side of peripersonal space? Even though left hemispace may not have been activated, the left side of the body was activated. One possibility is that reciprocal activation of more than one corresponding spatial sector of closely linked neuronal maps in the brain must occur in order to overcome the deficit in representing the left side of space. In other words, cueing or recruitment of the hemispatial system was inadequate on its own. The same applies for the hemi-corporeal ('personal') system. Only when both systems were activated simultaneously did some improvement of spatial perception of the left occur, possibly by reciprocal activation across related neuronal systems.

The above studies led to a series of treatment evaluations (Robertson et al., 1992; Robertson et al., 1998a) which involved making minimal movements of left limbs by using a Limb Activation Device (LAD). The LAD emitted random sounds, which the patient had to prevent or terminate by pressing a switch with some movement of a left limb. The results of this training were positive and daily ratings of mobility difficulties arising from the neglect showed improvements beginning with the onset of treatment. These ratings improved as the training commenced, and patients also showed improvements on standardized tests. The effectiveness of LAT has also been demonstrated in several controlled single-case-experimental design studies (Robertson & Hawkins, 1999; Samuel et al., 2000; Wilson et al., 2000).

LAT has also been subjected to a randomized-controlled trial (Kalra et al., 1997), though without use of the Limb Activation Device (LAD). In this last study, the neglect patients given LAT and standard inpatient rehabilitation had higher Barthel scores at twelve weeks (14 versus 12.5) and a significant reduction in median length of hospital stay (42 versus 66 days) compared to control patients receiving standard rehabilitation.

Recently, LAT has been subjected to a single-blind randomized controlled trial (Robertson, McMillan, Macleod, Edgeworth & Brock, submitted). Thirty-nine patients, who showed left unilateral neglect as a result of right hemisphere brain damage following CVA were randomly allocated to perceptual training plus LAT or to perceptual training alone. Both groups received twelve 45-minute training sessions over a twelve-week period. Thirty-six of the 39 patients were successfully followed

up blind at three months, a total of 32 were followed up blind at six months and 26 at 18-24 months. Outcome was assessed using a variety of standardized functional outcome and neuropsychological measures. LAT treatment was associated with significantly reduced unilateral neglect at three months post-treatment, and with significantly improved left-sided motor function at three, six and 18-24 months. The LAD can be used in the context of existing therapy with no increase in therapy time. This study shows that LAT can produce enduring improvements in unilateral neglect and in left-sided motor impairment in CVA patients suffering left unilateral neglect.

4.2.2 Other approaches to rehabilitation of neglect

4.2.2.1 Use of Prisms in neglect

French researchers (Rossetti et al., 1998) studied the effects of prism adaptation on patients with neglect. Distorting prisms over the eyes created an optical shift of ten degrees to the right for all visual input. Subjects had to point to stimuli in front of them, and received natural feedback through the mislocation movements they made. Over fifty such trials, they gradually learned to remap their motor responses to the new, distorted visual array. After removal of the goggles, they showed a significantly reduced neglect. This improvement lasted two hours, suggesting that the sensory-motor remappings produced by the prisms were not transient. In other words, the experience of having to recalibrate motor responses to a shifted visual array may have created relatively long-term plastic changes in synaptic connectivity in the impaired perceptuo-motor system of the lesioned hemisphere. This raises the possibility that the effects of the other types of rehabilitation described above may also rest at least in part on such plastic changes in the brain. Hence the observed therapeutic effects of rehabilitation may be based both on manipulation of activation in inhibited attentional networks, as well on plastic reorganization of the lesioned networks.

4.2.2.2 Interaction between the dorsal and ventral routes in neglect

The interaction of the brain's perceptual and motor systems is a topic of considerable current interest, particularly in the light of evidence that some visual information may have privileged access to the control of motor responses, yet not be available to awareness. The notion that the so-called dorsal stream may provide visual information for the motor system that is not available to awareness has received strong support

from a series of experiments by Milner and Goodale (1995). They have shown how cortically damaged patients who are incapable of consciously discriminating perceptual features (e.g. orientation) may nevertheless be able to make motoric responses that are sensitive to these features.

In the light of these results, Robertson and colleagues (Robertson et al., 1995a; Robertson et al., 1997b) predicted that the manifestation of unilateral neglect could be altered by changing the purpose of a reaching response. In their first experiment, ten neglect patients were tested in two conditions. In the first condition, patients were asked to point to the centre of a metal rod, while in the second condition they were asked to reach for the metal rod with a pincer grip of forefinger and thumb as if to pick it up so that it was balanced. The perceived middle was significantly further to the right in the pointing condition than in the reaching condition. In a second experiment, thirteen neglect patients pointed to the centre of a rectangular box with a lid that could swivel. They were then asked to place a coin at the centre of the lid, in a position sufficiently central to prevent the lid tilting and the coin falling into the box (in fact, unknown to the patients, the lid was fixed). In this experiment, patients showed less neglect when placing the coin in the perceived middle of the lid than when pointing to the perceived middle.

The result of these two experiments suggest that prehension movements towards objects allow ‘leakage’ of information about their spatial extent, via an apparently unaffected stream of information available for motor-manipulative responses. These findings have subsequently been replicated by Edwards and Humphreys (1999). This finding is compatible with data showing that while a conscious, ‘ventral’ representation of a stimulus can contaminate or override the short-lived motor representation, no such reciprocal influence seems to occur (Rossetti, 1998). In other words, this latter finding is compatible with data showing that activation of the dorsal stream appears to have effects on the ventral stream, a finding which was supported in a subsequent quasi- rehabilitation study (Robertson et al., 1997b).

In this study, people suffering from unilateral left neglect were actually encouraged to *pick up* rods so they would remain balanced. This activity not only facilitates the putative 'crosstalk' between the dorsal and ventral systems repeatedly, but also induces perceptual conflict in neglect patients: even though reaching to grip reduced neglect, their grip was still biased to the right of centre. Hence when they

picked up the rod at the point which visually seemed to them to be the centre, they would experience contradictory feedback from both the proprioceptive and visual modalities showing that this was not in fact the case. Robertson et al. therefore predicted short-term improvements in neglect as a result of a brief number of such exposures. Indeed, significant short-term improvements were found on neglect tasks after subjects experienced proprioceptive and other feedback discrepant from the judgments they made on the basis of visual information alone. Robertson and colleagues are currently studying whether extended training of this type produces more enduring improvements in neglect.

4.2.2.3 Manipulating egocentric space

The rightward spatial bias in neglect patients has also been explained in terms of a disturbance of the central transformation process that converts peripheral sensory input into an egocentric, body-centred co-ordinate system (Karnath et al., 1991; Karnath et al., 1993; Karnath, 1994; Karnath, 1995). Karnath and co-workers suggested that in neglect patients a systematic error in this co-ordinate transformation system results in deviation of the spatial reference frame to the ipsilateral side. Some rehabilitation methods have been homing in on manipulating the subjective body midline position in order to reduce neglect symptoms.

Karnath et al. (1993) showed that manipulating proprioceptive input by vibrating the posterior neck muscles or by turning the trunk 15° to the left reduced neglect symptoms compared to vibrating the left-hand muscles, which had no effect on neglect. These data were interpreted as showing that incoming proprioceptive information from the left neck muscles produced a leftward shift in the patients' subjective position of the sagittal midplane thus reducing neglect symptoms.

Another method that can temporarily reduce the rightward bias in neglect patients is caloric stimulation. A subjective sensation of displacement can be achieved by pouring iced water into the left ear canal or warm water in the right ear canal. In many cases this leads to a temporary improvement of unilateral neglect, which in most cases lasts 15-20 minutes. Studies of caloric stimulation have shown short-lasting facilitation of eye- and head turning towards the contralateral side (Cappa et al., 1987; Rubens, 1985). Although the effects of this technique are very limited in duration and may result in long lasting diminished responsiveness to repeated

stimulation, it may provide a useful tool in rehabilitation of neglect by facilitating attention to stimuli in the neglected side of space during training.

A third way to improve awareness of contralateral space by modulating patients' subjective body orientation is transcutaneous electrical nerve stimulation (TENS). TENS consists of electrical impulses delivered by surface stimulation electrodes that generate a tingling sensation. In an experiment by Vallar et al. (1995), neglect patients received TENS applied to the neck. While stimulation of the left side of the neck improved performance on a letter cancellation task in thirteen out of fourteen patients, right neck stimulation worsened performance in nine patients. In a following experiment using TENS, stimulation of both the left hand and the left neck had comparable effects on neglect in six patients. A number of studies have shown that TENS can (transiently) improve symptoms associated with neglect (Guariglia et al., 1998; Guariglia et al., 2000a; Guariglia et al., 2000b; Karnath, 1995; Vallar et al., 1996).

There are several ways to interpret these results. One possible interpretation attributes the effects of TENS to the correction of the systematic error in the co-ordinate transformation system in neglect patients (Karnath, 1995). However, there is also data suggesting that TENS produces a non-specific activation of the right hemisphere by increasing arousal (Vallar et al., 1995). The relationship between arousal and neglect will be discussed in the following paragraph.

4.2.2.4 Arousal and neglect

Our analysis of the cognitive architecture of spatial attention has so far suggested two types of rehabilitative process - joint activation of mutually facilitatory networks and reduction of inhibitory competition. Another example of the mutual facilitation process draws on evidence for the lawful interaction of two apparently very different types of cognitive process - the arousal/sustained attention systems of the brain on one hand, and the spatial attention system on the other. Heilman and colleagues showed the predominance of the right hemisphere in mediating this generalized enhanced responsivity/activation to stimuli (Heilman et al., 1978; Heilman & Van den Abell, 1979). Patients with right hemisphere lesions were hypoaroused relative to left hemisphere lesioned patients. For example, absent galvanic skin response (GSR) to pictures of emotionally arousing scenes (such as of mutilated hands and battles) was almost absent.

As we mentioned before, sufferers from both left- and right-sided stroke are equally likely to suffer distortions of spatial attention in the immediate post-stroke period (De Kort, 1996). Quite rapidly however, the pattern becomes unbalanced with right hemisphere patients forming the overwhelming majority of those who show chronic spatial deficits. There is considerable evidence now to suggest that the persistence of unilateral spatial neglect is very strongly determined by deficits in a non-spatial, partly right-hemisphere-based system for maintaining arousal in the brain. In support of this view, researchers found that non-lateralized attentional deficits are extremely powerful predictors of persisting unilateral neglect (Robertson et al., 1997a), and that the most powerful anatomical predictor of persisting neglect is a lesion to the paraventricular white matter in the right temporal lobe, the likely location of fibres projecting up to the parietal and frontal lobes from the midbrain arousal systems (Samuelsson et al., 1997; Samuelsson et al., 1998)

Robertson et al. (Robertson et al., 1998b) put these correlational links between arousal and neglect to experimental test. They predicted that phasically increasing the patients' alertness should transiently ameliorate the spatial bias in perceptual awareness, and indeed the results provided the first direct confirmation of this prediction. The task required right-hemisphere neglect patients to judge whether a left visual event preceded a comparable right event, or vice-versa. On average, neglect patients became aware of left events half a second later than right events. This dramatic spatial imbalance in the timecourse of visual awareness could be reversed if a warning sound alerted the patients phasically. Even a sound on the right dramatically accelerated the perception of left visual events. A non-spatial alerting intervention can thus overcome disabling spatial biases in perceptual awareness after brain injury.

In a clinical-experimental corollary of the above study, Robertson and colleagues attempted directly to rehabilitate sustained attention in eight patients with unilateral left neglect following right hemisphere lesions (Robertson et al., 1995b). Patients received training in the context of a number of tasks: sorting coins, sorting cards, or sorting shapes of different colours, sizes, and shapes. These tasks did not emphasize lateralized scanning. The patients' attention was repeatedly drawn to the task by combining a loud noise with an instruction to attend. They were then gradually taught to 'take over' this alerting procedure in order to improve their

internal, or endogenous, control of attention by 'talking themselves through the task'. The training had a fixed series of stages:

1. The patient carried out one of the tasks. His/her errors were pointed out.
2. The nature of problems with sustained attention and alertness and the rationale for the training strategy were explained to the patient in colloquial terms, namely, that it is possible to use undamaged parts of the brain (i.e. the language system) to modulate and activate the impaired parts of the brain – namely the sustained centres of the right hemisphere.
3. The patient had to carry out the task again, but now the trainer knocked loudly and unpredictably on the desk on average every 20-30 s and said "Attend!" in a loud voice.
4. After several repetitions of step 3, the patient said "Attend!" when the trainer knocked on the desk, and the trainer said nothing.
5. After several repetitions of step 4, the patient was cued rap the desk at approximately the same frequency as the trainer had. The patient was required to say "Attend!" out loud at the same time.
6. The patient now rapped the desk and said "Attend!" subvocally.
7. The patient now simply signalled whenever he/she was 'mentally' rapping the desk and telling him/herself to "pay attention". If this was not done, he or she was cued by the trainer to implement the strategy.
8. Finally, the patients were told about the desirability of trying to apply this strategy habitually in everyday life situations, so that they could monitor their attention to any particular task.

Not only were there improvements in sustained attention among this group of eight patients, there were also very significant improvements on spatial neglect over and above those expected from natural recovery. This study shows that the spatial bias in unilateral neglect can be briefly reduced using exogenous alerting stimuli, but that it may also be possible to reduce this bias endogenously, using self-initiated alerting mechanisms.

4.3 Concluding remarks

The fact that symptoms of neglect vary from patient to patient and may even be subject to change over time within each patient can make it very hard for rehabilitation therapists to decide which method should be applied to an individual patient, let alone to formulate a single superior modus operandi applicable to all patients. Furthermore, in clinical practice rehabilitation of neglect is often hampered by patients' lack of awareness with regard to their symptoms. Anosodiaphoria (an inappropriate lack of concern about impairments) and anosognosia (a complete denial of symptoms) are commonly found in association with personal and peripersonal neglect. Making a patient aware of his / her deficit is often the key to successful rehabilitation.

In the past decades numerous behavioural strategies and more theory-driven methods have been developed to rehabilitate neglect. When comparing these methods some considerations should be taken into account. Firstly, some interventions are aimed mainly at overcoming specific symptoms of neglect and are limited to a specific domain. In general, the effects of these methods are also task-specific and do not generalize over the entire domain of ADL functioning, let alone change the underlying mechanisms of neglect. On the other hand, methods aiming to improve the wider spectrum of neglect are much harder to evaluate, since both training and effect are not limited to specific tasks or tests. Secondly, some methods appear to be effective only when training is very intensive. In practice, only a restricted number of patients may benefit from these methods since both therapy resources and the patient's condition may not allow such a level of intensity. Thirdly, it appears that some of the most potent rehabilitation effects are also the most transient. Behavioural changes lasting for periods of hours are not in themselves clinically useful, unless they can be demonstrated to endure over much longer periods of time. Nevertheless, careful experimental investigations of short-term changes, particularly if they are tied into strong theoretical models of underlying cognitive function, are of considerable value in the development of theoretically based, yet clinically-important, rehabilitation methods.

It is also important to note that not all improvements in neglect produced by the different manipulations we described may be based on experience-dependent structural changes in brain circuits. Where such effects are long lasting, however,

there is a much greater chance that the observed differences are attributable to such mechanisms. Pizzamiglio and colleagues have carried out one of the very few PET studies of brain reorganization following rehabilitation. In three patients with unilateral neglect following primarily subcortical lesions, they found that recovery was mainly associated with cerebral activation in right hemisphere cortical regions similar to those observed in normal subjects (Pizzamiglio et al., 1998). While there have been too few studies carried out on the cerebral effects of rehabilitation to compare with studies on natural recovery, this latter study suggests that under certain circumstances, the mechanisms of natural recovery and of 'guided', rehabilitated recovery may be quite similar.

References

Antonucci, G., Guariglia, C., Judica, A., Magnotti, L., Paolucci, S., Pizzamiglio, L. et al. (1995). Effectiveness of neglect rehabilitation in a randomized group study. *Journal of Clinical and Experimental Neuropsychology, 17,* 383-389.

Berti, A. & Rizzolatti, G. (1992). Visual processing without awareness: evidence from unilateral neglect. *Journal of Cognitive Neuroscience, 4,* 345-351.

Bisiach, E. & Vallar, G. (1988). Hemineglect in humans. In F.Boller & J. Grafman (Eds.), *Handbook of neuropsychology (Vol. 1)* (pp. 195-222). Amsterdam: Elsevier.

Cappa, S. F., Sterzi, R., Vallar, G., & Bisiach, E. (1987). Remission of hemineglect and anosognosia during vestibular stimulation. *Neuropsychology, 5,* 204.

Damasio, A. R., Damasio, H., & Chui, H. C. (1980). Neglect following damage to frontal lobe or basal ganglia. *Neuropsychologia, 18,* 123-132.

De Kort, P. (1996). *Neglect, een klinisch onderoek naar halfzijdige verwaarlozing bij patienten met een cerebrale bloeding of infarct.* RijksUniversiteit Groningen.

Diller, L. & Weinberg, J. (1977). Hemi-inattention in rehabilitation: The evolution of a rational remediation program. In E.A.Weinstein & R. O. Friedland (Eds.), *Hemi-inattention and hemisphere specialization* (pp. 63-82). New York: Raven.

Edwards, M. G. & Humphreys, G. W. (1999). Pointing and grasping in unilateral visual neglect: effect of on-line visual feedback in grasping. *Neuropsychologia, 37,* 959-973.

Gialanella, B. & Mattioli, F. (1992). Anosognosia and extrapersonal neglect as predictors of functional recovery following right hemisphere stroke. *Neuropsychological Rehabilitation, 2,* 169-178.

Gouvier, W., Bua, B., Blanton, P., & Urey, J. (1987). Behavioral changes following visual scanning training: observation in five cases. *International Journal of Clinical Neuropsychology, 9,* 74-80.

Guariglia, C., Coriale, G., Cosentino, T., & Pizzamiglio, L. (2000a). TENS modulates spatial reorientation in neglect patients. *Neuroreport, 11,* 1945-1948.

Guariglia, C., Coriale, G., Cosentino, T., & Pizzamiglio, L. (2000b). TENS modulates spatial reorientation in neglect patients [In Process Citation]. *Neuroreport, 11,* 1945-1948.

Guariglia, C., Lippolis, G., & Pizzamiglio, L. (1998). Somatosensory stimulation improves imagery disorders in neglect. *Cortex, 34,* 233-241.

Heilman, K. M., Schwartz, H. D., & Watson, R. T. (1978). Hypoarousal in patients with the neglect syndrome and emotional indifference. *Neurology, 28,* 229-232.

Heilman, K. M. & Van den Abell, T. V. B. (1979). Right hemisphere dominance for mediating cerebral activation. *Neuropsychologia, 17,* 315-321.

Kalra, L., Perez, I., Gupta, S., & Wittink, M. (1997). The influence of visual neglect on stroke rehabilitation. *Stroke, 28,* 1386-1391.

Karnath, H. O. (1994). Subjective body orientation in neglect and the interactive contribution of neck muscle proprioception and vestibular stimulation. *Brain, 117 (Pt 5),* 1001-1012.

Karnath, H. O. (1995). Transcutaneous electrical stimulation and vibration of neck muscles in neglect. *Experimental Brain Research, 105,* 321-324.

Karnath, H. O., Christ, K., & Hartje, W. (1993). Decrease of contralateral neglect by neck muscle vibration and spatial orientation of trunk midline. *Brain, 116 (Pt 2),* 383-396.

Karnath, H. O., Ferber, S., & Himmelbach, M. (2001). Spatial awareness is a function of the temporal not the posterior parietal lobe. *Nature, 411,* 950-953.

Karnath, H. O., Schenkel, P., & Fischer, B. (1991). Trunk orientation as the determining factor of the 'contralateral' deficit in the neglect syndrome and as the physical anchor of the internal representation of body orientation in space. *Brain, 114 (Pt 4),* 1997-2014.

Ladavas, E., Berti, A., Ruozzi, E., & Barboni, F. (1997). Neglect as a deficit determined by an imbalance between multiple spatial representations. *Experimental Brain Research, 116,* 493-500.

Milner, A. D. & Goodale, M. A. (1995). *The visual brain in action*. Oxford: Oxford University Press.

Pizzamiglio, L., Antonucci, G., Judica, A., Montenero, P., Razzano, C., & Zoccolotti, P. (1992). Cognitive rehabilitation of the hemineglect disorder in chronic patients with unilateral right brain damage. *Journal of Clinical and Experimental Neuropsychology, 14,* 901-923.

Pizzamiglio, L., Perani, D., Cappa, S. F., Vallar, G., Paolucci, S., Grassi, F. et al. (1998). Recovery of neglect after right hemispheric damage: H2(15)O positron emission tomographic activation study. *Archives of Neurology, 55,* 561-568.

Rizzolatti, G. & Berti, A. (1990). Neglect as a neural representation deficit. *Revue Neurologique, 146,* 626-634.

Rizzolatti, G. & Berti, A. (1993). Neural mechanisms of spatial neglect. In I.H.Robertson & J. C. Marshall (Eds.), *Unilateral neglect: Clinical and experimental studies* (pp. 87-106). Hove, U.K.: Erlbaum.

Robertson, I. H., Gray, J. M., Pentland, B., & Waite, L. J. (1990). Microcomputer-based rehabilitation for unilateral left visual neglect: a randomized controlled trial. *Archives of Physical Medicine and Rehabilitation, 71,* 663-668.

Robertson, I. H. & Hawkins, K. (1999). Limb activation and unilateral neglect. *Neurocase, 5,* 153-154.

Robertson, I. H., Hogg, K., & McMillan, T. M. (1998a). Rehabilitation of unilateral neglect: improving function by contralesional limb activation. *Neuropsychological Rehabitation, 8,* 19-29.

Robertson, I. H., Manly, T., Beschin, N., Daini, R., Haeske, D. H., Homberg, V. et al. (1997a). Auditory sustained attention is a marker of unilateral spatial neglect. *Neuropsychologia, 35,* 1527-1532.

Robertson, I. H., Mattingley, J. B., Rorden, C., & Driver, J. (1998b). Phasic alerting of neglect patients overcomes their spatial deficit in visual awareness. *Nature, 395,* 169-172.

Robertson, I. H., Nico, D., & Hood, B. M. (1995a). The intention to act improves unilateral left neglect: two demonstrations. *Neuroreport, 7,* 246-248.

Robertson, I. H., Nico, D., & Hood, B. M. (1997b). Believing what you feel: using proprioceptive feedback to reduce unilateral neglect. *Neuropsychology., 11,* 53-58.

Robertson, I. H. & North, N. (1992). Spatio-motor cueing in unilateral left neglect: the role of hemispace, hand and motor activation [see comments]. *Neuropsychologia, 30,* 553-563.

Robertson, I. H. & North, N. (1993). Active and passive activation of left limbs: influence on visual and sensory neglect. *Neuropsychologia, 31,* 293-300.

Robertson, I. H., North, N. T., & Geggie, C. (1992). Spatiomotor cueing in unilateral left neglect: three case studies of its therapeutic effects. *Journal of Neurology, Neurosurgery and Psychiatry, 55,* 799-805.

Robertson, I. H., Tegner, R., Tham, K., Lo, A., & Nimmo-Smith, I. (1995b). Sustained attention training for unilateral neglect: theoretical and rehabilitation implications. *Journal of Clinical and Experimental Neuropsychology, 17,* 416-430.

Rossetti, Y. (1998). Implicit short-lived motor representations of space in brain damaged and healthy subjects. *Consciousness and Cognition, 7,* 520-558.

Rossetti, Y., Rode, G., Pisella, L., Farne, A., Li, L., Boisson, D. et al. (1998). Prism adaptation to a rightward optical deviation rehabilitates left hemispatial neglect. *Nature, 395,* 166-169.

Rubens, A. B. (1985). Caloric stimulation and unilateral visual neglect. *Neurology, 35,* 1019-1024.

Samuel, C., Louis-Dreyfus, A., Kaschel, R., Makiela, E., Troubat, M., Anselmi, N. et al. (2000). Rehabilitation of severe unilateral neglect by visuo-spatial cueing: Two single case studies. *Neuropsychological Rehabilitation,* 385-399.

Samuelsson, H., Hjelmquist, E. K., Jensen, C., Ekholm, S., & Blomstrand, C. (1998). Nonlateralized attentional deficits: an important component behind persisting visuospatial neglect? *Journal of Clinical and Experimental Neuropsychology, 20,* 73-88.

Samuelsson, H., Jensen, C., Ekholm, S., Naver, H., & Blomstrand, C. (1997). Anatomical and neurological correlates of acute and chronic visuospatial neglect following right hemisphere stroke. *Cortex, 33,* 271-285.

Sprague, J. M. (1966). Interaction of cortex and superior colliculus in mediation of visually guided behavior in the cat. *Science, 153,* 1544-1547.

Vallar, G. (1993). The anatomical basis of spatial neglect in humans. In I.H.Robertson & J. C. Marshall (Eds.), *Unilateral Neglect: Clinical and Experimental Studies* (Hove, Sussex: Lawrence Erlbaum Associates.

Vallar, G. (2001). Extrapersonal visual unilateral spatial neglect and its neuroanatomy. *Neuroimage, 14,* S52-S58.

Vallar, G. & Perani, D. (1986). The anatomy of unilateral neglect after right-hemisphere stroke lesions. A clinical/CT-scan correlation study in man. *Neuropsychologia, 24,* 609-622.

Vallar, G., Rusconi, M. L., Barozzi, S., Bernardini, B., Ovadia, D., Papagno, C. et al. (1995). Improvement of left visuo-spatial hemineglect by left-sided transcutaneous electrical stimulation. *Neuropsychologia, 33,* 73-82.

Vallar, G., Rusconi, M. L., & Bernardini, B. (1996). Modulation of neglect hemianesthesia by transcutaneous electrical stimulation. *Journal of the International Neuropsychological Society, 2,* 452-459.

Vuilleumier, P., Hester, D., Assal, G., & Regli, F. (1996). Unilateral spatial neglect recovery after sequential strokes. *Neurology, 46,* 184-189.

Watson, R. T. & Heilman, K. M. (1979). Thalamic neglect. *Neurology, 29,* 690-694.

Weinberg, J., Diller, L., Gordon, W. A., Gerstman, L. J., Lieberman, A., Lakin, P. et al. (1977). Visual scanning training effect on reading-related tasks in acquired right brain damage. *Archives of Physical Medicine and Rehabilitation, 58,* 479-486.

Wilkins, A. J., Shallice, T., & McCarthy, R. (1987). Frontal lesions and sustained attention. *Neuropsychologia, 25,* 359-365.

Wilson, F. C., Manly, T., Coile, D., & Robertson, I. H. (2000). The effect of contralesional limb activation training and sustained attention training for self-care programmes in unilateralspatial neglect. *Restorative Neurology and Neuroscience, 16,* 1-4.

Section 3

Experimental studies

Chapter 5

Disproportionate impairment of recognition of close family members: a case of selective prosopagnosia or a mild variant of Capgras delusion?

Joost Heutink, Wiebo H. Brouwer, Evelien Kums, Andrew W. Young & Anke Bouma

Abstract

In this study, we describe 62-year old female patient (JS) with disproportionately impaired recognition of close family members compared to other familiar people after ischaemic stroke. JS simultaneously displays some characteristics of prosopagnosia and some characteristics of Capgras delusion. JS has impaired recognition of familiar faces, a characteristic of prosopagnosia. However, JS also has delusional believes about the appearance of emotionally significant people, which is one of the features of Capgras delusion. Differences between Capgras delusion and prosopagnosia have recently been explained in terms of a discrepancy between covert and overt face recognition. We assessed overt and covert face recognition of JS and age-matched controls on a face recognition task consisting of pictures of close family members, celebrities and unfamiliar faces. JS was less accurate and slower in response to family, compared to celebrities and unfamiliar faces. Although, compared to controls, JS had lower overall skin conductance responses (SCRs) to faces, her SCR amplitude to family was higher than to unfamiliar faces. We discuss whether JS has a distinct form of prosopagnosia or Capgras delusion and consider the implications for the currently most influential explanatory model of face recognition.

5.1 Introduction

The way we interact with other people depends on how well we know them. In order to determine whether we know an individual or not, and whether someone is a good friend, a family member or a vague acquaintance, we strongly rely on brain mechanisms that underlie quick and accurate face recognition. Brain lesions that affect this ability for face identification therefore severely impair interactions with our social environment.

Several models for face perception have been proposed, of which Bruce & Young's model (1986) has proven to be very influential. According to this linear model, at the first stage of normal face perception, structural encoding takes place, during which the non-changing facial parts such as size and position of the nose, eyes and mouth are processed. At the next stage, so-called face recognition units (FRUs) provide a familiarity guess. The following stage uses person identity nodes (PINs) to provide a biographical context for the familiar face (such as profession). According to the model, it is only during the last stage that the name of the familiar person is provided.

During the last ten years, some modifications and additions to Bruce and Young's model have been put forward (see Figure 5.1 for an overview of Bruce and Young's initial model and the later revisions proposed by other authors). These modifications were prompted by studies of two disorders of face perception: Capgras delusion and Prosopagnosia. *Capgras delusion* is a rare and fascinating disorder of face perception and recognition. Capgras delusion refers to the belief that close acquaintances, such as parents or children, have been replaced by impostors, robots or aliens (Ellis et al., 1997; Hirstein & Ramachandran, 1997). Patients with Capgras delusion admit that these 'impostors' really look like their acquaintance, but in fact are not identical to this person. Capgras delusion can occur in idiopathic psychiatric illness such as schizophrenia as well as after acquired brain injury, with lesions in the frontal, temporal or parietal lobes (Bourget & Whitehurst, 2004). Several cases of Capgras delusion have been described in the literature, of which Hirstein and Ramachandran's patient DS (Hirstein & Ramachandran, 1997) and Ellis and Lewis et al.'s patient BP (Ellis et al., 2000) are probably the best known.

Prosopagnosia is less rare than Capgras delusion and refers to the complete inability to recognize previously familiar faces (Damasio, 1985). Most patients with

prosopagnosia have bilateral damage to the inferior occipitotemporal cortex, in particular the lingual and fusiform gyri (Damasio et al., 1982; Damasio, 1985), but there are also numerous reports of prosopagnosia after unilateral right-hemisphere lesions (DeRenzi et al., 1994).

The most important recent contribution to Bruce and Young's model is the distinction between overt (explicit) recognition and covert (implicit) face recognition. Evidence suggests that, although prosopagnosia patients have severely impaired explicit recognition of familiar faces, covert face recognition may still be intact. For instance, prosopagnosia patients show enhanced skin conductance responses (SCRs) to familiar faces compared to unfamiliar faces (Bauer, 1984; Tranel et al., 1995). Covert face recognition has also been established in behavioural experiments, such as tasks involving face-name associations (De Haan et al., 1987; De Haan et al., 1991) and priming tasks (Barton et al., 2004; Young et al., 1988).

It has been suggested that Capgras delusion might be the mirror image of prosopagnosia (Ellis & Young, 1990). Ellis and Young (1990) proposed that Capgras delusion results from an intact overt face recognition coupled with a damaged covert face recognition system. Indeed, in five psychiatric patients with Capgras delusion, Ellis et al. (1997) showed reduced SCRs to familiar faces, while SCRs to a loud noise were normal. Hirstein and Ramachandran (1997) and Ellis et al. (2000) showed a similar effect in single patients with Capgras delusion. Prosopagnosia thus would involve a disorder in overt face recognition, while Capgras delusion would involve impaired covert face recognition. It has been argued however, that the absence of covert recognition on its own is not *enough* to produce the crucial hallmark of Capgras delusion, namely the simultaneous recognition of a face and the denial of its authenticity (Hirstein & Ramachandran, 1997). In other words, the lack of 'familiar feeling' by itself is not considered to be sufficient to lead to the delusion that a significant other has been replaced by an impostor. Therefore, Ellis et al. proposed a further addition to the model, namely that the covert, affective recognition system and the overt recognition system must be integrated by an additional module which compares the expected affective response with the actual affective response and which generates an attribution (Ellis & Lewis, 2001).

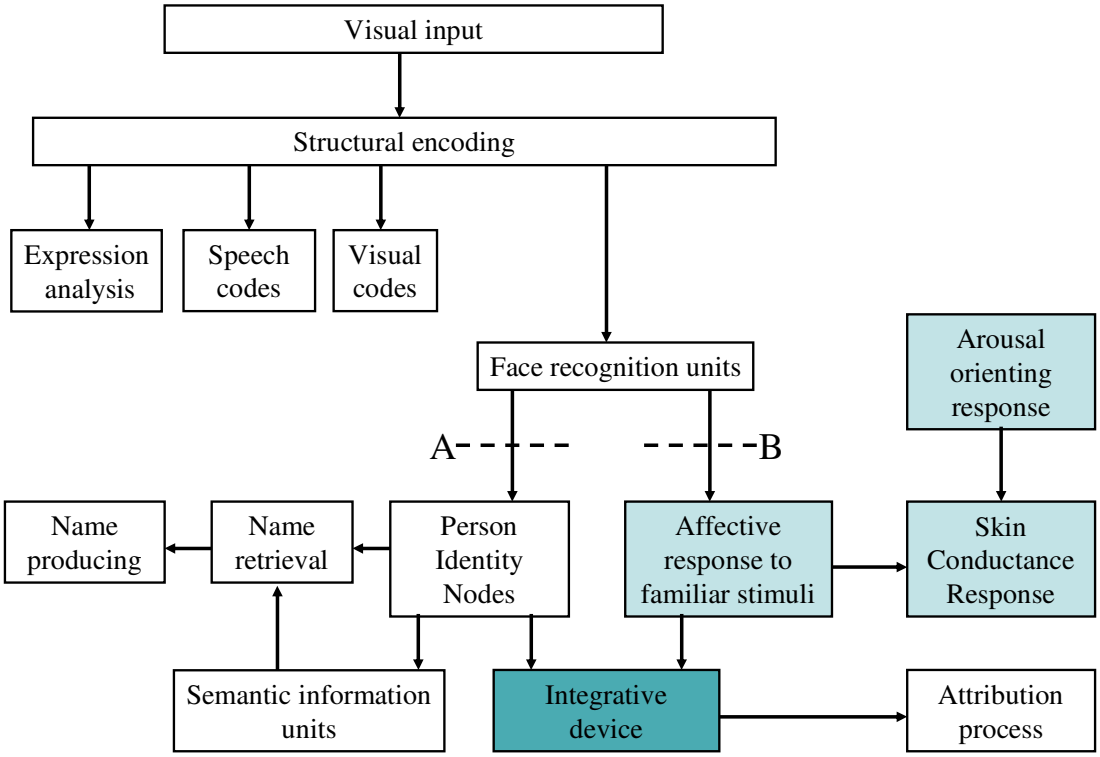


Figure 5.1. An adaptation of Bruce and Young's model of face recognition (Bruce & Young, 1986) to explain recognition and misidentification syndromes, as proposed by Ellis & Lewis (2000). The white units reflect Bruce and Young's original model. The gray coloured units are additions as proposed by Breen et al. (2000b) and Ellis and Lewis (2001). The model proposes two routes of face recognition, covert and overt, which are compared by an integrative device. A disconnection at location A will lead to impaired overt face recognition with intact covert recognition and autonomic responses, as is the case in prosopagnosia. A disconnection a location B will lead to loss of autonomic response with intact overt recognition. The conflict that arises in the integrative device as a result of this incongruence leads to the attribution that a close acquaintance has been replaced by an impostor, as is the case in Capgras delusion.

In this paper, we present a 62-year old female patient (JS) with impaired recognition of faces after an ischaemic stroke. Intriguingly, and unlike prosopagnosia, this impairment was most severe for recognition of her closest family members, while recognition of celebrities and more distant family members and acquaintances was mostly unimpaired. JS does not believe that her closest relatives have been replaced by impostors – the crucial hallmark of Capgras delusion – but she reports that they look different or even repulsive. Similar to Capgras delusion however, the disorder appears to be limited to recognition of the closest relatives and not to emotionally-

neutral acquaintances. JS thus simultaneously displays some characteristics of prosopagnosia and some characteristics of Capgras delusion. To the best of our knowledge, this phenomenon has not been described earlier.

The main goal of this study was to objectify the nature of the face perception disorder in JS. As a dissociation between covert and overt recognition is essential in the aforementioned explanatory model of prosopagnosia and Capgras delusion, we investigated accuracy of recognition, response times and electrophysiological responses (SCR) to presentation of images of close relatives, celebrities and unfamiliar faces. Performance of JS was compared to three controls which were matched on gender, age and family size.

5.2 Method

5.2.1 Case JS

Medical History: JS is a right-handed female aged 62. Twelve months before participating in this study JS was referred to the Neurology unit of the University Medical Centre Groningen (UMCG). Initial CT showed an ischaemic infarct of the posterior (temporal) branch of the right middle cerebral artery. Structural MRI (9 months post-stroke) showed a lesion in the occipitotemporal area, mostly affecting the middle temporal gyrus, while leaving the lower temporal gyrus intact. MRI also showed older lesions, one in the right-hemisphere frontal area just above the anterior part of the putamen and deep white-matter lesions in the left temporal lobe. Images of the MRI are displayed in Figure 5.2.

At neurological examination during the subacute stage, JS was alert and well oriented; she showed visual extinction for the left hemifield, problems with facial recognition, no tactile extinction, no aphasia and a MMSE score of 29. JS reported difficulties recognizing her family members who visited her in the hospital. She was unable to recognize one of her daughters, with whom she had very frequent contact. Another daughter however, which JS hadn't seen in a period of eight years, was recognized without any problem. During her stay in the hospital, JS refused her grandchildren to sit on her lap because she believed they looked repulsive. Later assessment, three months post-stroke showed that JS had no homonymous hemianopia (Goldmann perimetry showed intact visual field). Visual acuity was 1.0 (20/20) for

both eyes en ocular movements were normal. There were no indications of impaired colour vision (Ishihara colour plates).

Neuropsychological assessment: Ten days after admission to the hospital, JS underwent neuropsychological testing. JS scored normal on tests for unilateral neglect (Balloons test and Bells test). On the Visual Object and Space Perception Battery (VOSP), JS scored two points below cut-off on the sub-test incomplete letters, indicating mild integrative agnosia. On the Facial Expressions of Emotion: Stimuli and Test (FEEST), her total score was 32 (8 below cut-off), indicating impaired perception of emotional facial expressions. Except for sadness (2 below cut-off), JS did not score below cut-off on the discrete emotions of the FEEST. JS' score on the short form of the Benton Test of Facial Recognition was 18 (corrected long form score: 38) indicating moderately impaired facial perception.

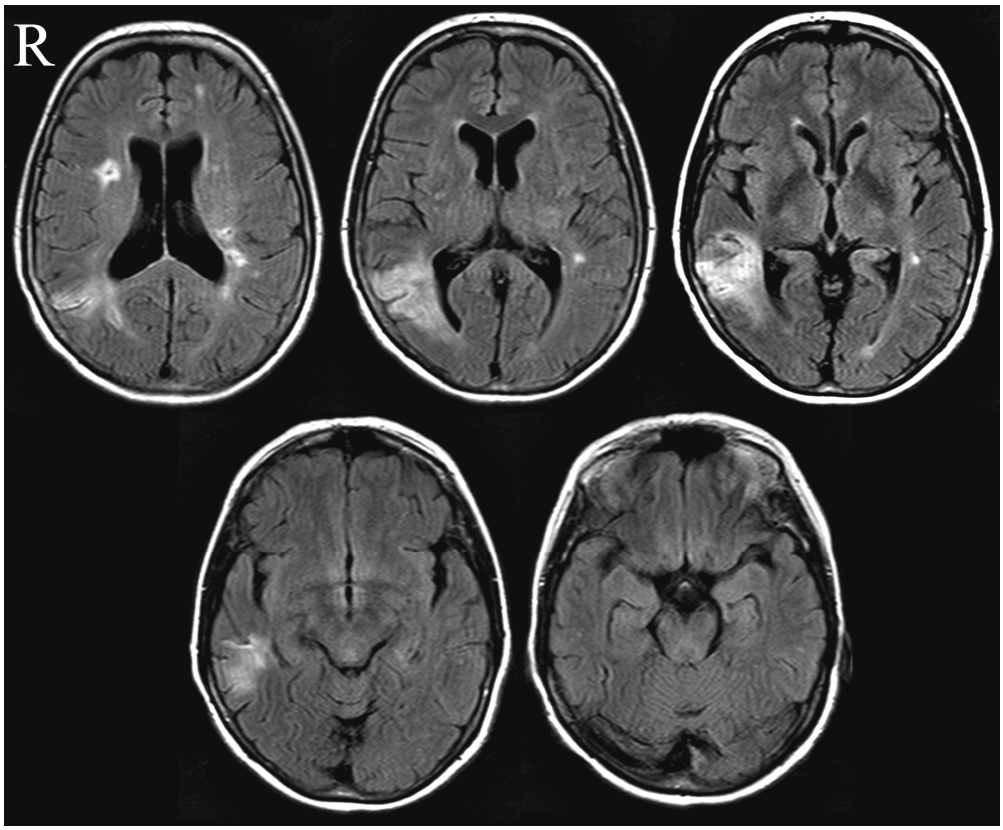


Figure 5.2. Axial slices of MRI (flare) taken 9 months post-stroke. Left side of the image = Right side of the brain

During neuropsychological assessment, JS was shown a series pictures of family members, celebrities and unfamiliar people. JS had great difficulty recognizing close family members and friends, while there were no apparent problems in identifying celebrities. Family pictures of the investigator (JH) were immediately recognized as unfamiliar strangers and pictures of look-alikes of celebrities were not mistaken for the real celebrities. JS reported that her family members looked strange or even repulsive to her. She told that facial proportions were distorted, although she was unable to tell in which way the proportions were altered. Her grandchildren looked to her as if they had extreme overweight and had an extremely tanned skin as if they had spent too much time in a solarium. When she was asked how it was possible that identifying family members of the investigator as strangers took no effort, while identifying her own family members took much more time, she answered: "That's because these strangers look like normal people. The others don't."

Strikingly, when shown pictures of Adolph Hitler and of Osama bin Laden, JS identified them as very poor look-alikes who should have made more effort to look like the 'real' people. When asked, JS told she could identify Hitler's 'look-alike' by his moustache. Nevertheless, when questioned why she thought he was such a poor look-alike she replied: "His moustache really doesn't look anything like Adolph Hitler's – his moustache was much more well-groomed."

5.2.2 Control subjects

Three female right-handed control subjects participated in this study. The controls had roughly the same age as JS (48, 54 and 58 years old) and all had a large family (like JS). The controls had no history of neurological damage or psychiatric illness.

5.2.3 Design

Stimuli consisted of greyscale images of close relatives, celebrities and unfamiliar people. Images were sized 20 x 15 cm and presented on a 17 inch monitor. All images had roughly the same luminance and the same resolution.

Subjects were seated at 1 meter distance from the screen. Stimuli were presented in three blocks, each consisting of 60 trials.

Each trial consisted of a central warning signal (*: 300-500 ms) followed by the stimulus (1000 ms). After the stimulus a question mark appeared (?: 500 ms) at which point the subject could give a response.

Subjects responded by pressing a yes or no button to indicate whether they recognized the person presented on the screen or not. Subjects were instructed not to press as quickly as possible, but to press at the moment that they were fairly confident about their response. This procedure was chosen to avoid a large proportion of errors. The duration of the interval between each trial was determined by the researcher in order to allow SCR to return to baseline level before presentation of the next trial.

In each block, consisting of 60 trials, 30 images of unfamiliar people, 15 images of close relatives and 15 images of celebrities were presented in random order. The images were chosen as follows. Several weeks before the experiment took place, all subjects completed a list in which they named the 15 closest family members and in which they chose the names of 15 celebrities out of a list of 50 national and international politicians, actors, etc. For each of the selected celebrities, three pictures were taken from the internet, while all indicated family members were photographed three times by the researchers (JH and EK) or a relative of the subject. The background of the pictures was removed to exclude contextual information. The photographs of close relatives of each subject were used in the category unfamiliar people for the other subjects. In each block, one of the three photographs of each selected celebrity or close relative was presented. Each parallel block thus contained different images of the same people.

5.2.4 Autonomic responses

Autonomic responses to faces were assessed by measuring SCRs to the presentation of the stimuli. Two Ag/AgCl electrodes were attached to the middle phalanges of the index and middle finger of the nondominant left hand. Prior to the experiment, normal SCR response to arousal was established by asking subjects to breathe deeply and by loud clapping by the experimenter. SCRs were sampled at 1000 Hz and online reduced to a sample frequency of 100 Hz. SCR data was further analysed using BrainVision© software. The SCR signal was segmented into single trials with the start of the presentation of the stimulus as time zero.

After segmentation, a baseline correction was performed based on the average amplitude of 2000 ms preceding stimulus onset. Including baseline, each segment had a duration of 12000 ms. SCR amplitude, magnitude and peak latency were calculated. *SCR amplitude* is the average baseline to peak amplitude of SCRs of valid responses. Valid responses are responses with a rise in SCR of at least 0.01 microSiemens (μS)

within 10 seconds after stimulus onset. *SCR magnitude* is the average baseline to peak amplitude of SCRs with invalid responses (i.e. a rise in SCR below 0.01 μS) included.

To control for individual differences in the absolute size of SCR response, amplitudes of each subject were corrected for range. Next, SCR data were log-transformed in order to meet criteria for normal distribution. Because of habituation to stimuli, only SCR data obtained during the first block were analysed. Possibly due to a very callous skin structure, control subject 2 had a very low resting skin conductance (0.0071 μS) and hardly any rise in SCR amplitude could be related to stimulus presentation. Therefore, SCR data from control subject 2 was not included in the analysis.

5.2.5 Statistical analysis and contrasts

Statistical analysis was performed with SPSS (v 11.01). Fisher's exact test was used for comparison of the proportions of correct and incorrect responses. Analyses of response times, SCR amplitude, magnitude, and latency consisted of univariate ANOVA with the factors subject (JS or controls) and stimulus type (unfamiliar, celebrity and family) with a Helmert contrast for unfamiliar versus familiar (i.e. celebrity and family) and celebrity versus family. In case of a main effect for subject or an interaction between subject and stimulus type, further ANOVA was performed for JS and controls separately. Bonferroni correction was used for post-hoc pairwise comparisons.

5.3 Results

5.3.1 Response Accuracy

Table 5.1 shows proportion of correct responses, mean response times and standard deviations for correct responses in the recognition task. Controls had 97-99% accuracy on recognition of three types of stimuli. JS' proportion of incorrect responses to unfamiliar faces did not differ significantly from controls (Fisher exact test $p = 0.21$). Compared to controls, JS had a lower proportion of correct responses to celebrities (Fisher exact test $p < 0.001$) and family (Fisher exact test $p < 0.001$). JS was better at identifying pictures of celebrities than family (Fisher exact test $p < 0.05$).

Table 5.1. Proportion of correct responses, mean reaction times (in ms) and standard deviations for correct responses in the face recognition task

	Unfamiliar (n=90)	Celebrities (n=45)	Family (n=45)
JS			
RT	2519	2673	4800
SD	560	786	1849
%Correct	96%	76%	49%
Controls			
RT	1382	1246	1098
SD	263	230	218
%Correct	99%	99%	97%

5.3.2 Response times

Figure 5.3 shows mean response times and standard deviation of correct responses. JS had longer response times than controls, $F(1, 667) = 1651.0$, $p < 0.001$. An interaction between subject and stimulus type prompted separate analyses of JS and controls, $F(2, 677) = 216.84$, $p < 0.001$. Control participants' analysis showed a significant effect of stimulus type, $F(2, 528) = 60.91$, $p < 0.001$. Post-hoc comparison showed that responses of controls to familiar faces were faster than to unfamiliar faces ($p < 0.001$) and responses to family were faster than to celebrities ($p < 0.001$). For response times of JS, also a significant effect of stimulus type was found, $F(1, 139) = 54.77$, $p < 0.001$. JS responded more slowly to familiar faces than to unfamiliar faces ($p < 0.001$) and responses to family were slower than to celebrities ($p < 0.001$). JS' response times to celebrities and unfamiliar faces were not significantly different. Furthermore, there was no significant difference between response times to correct presses and incorrect presses, $t(178) = 0.912$, $p = 0.363$.

5.3.3 Autonomic Responses

Figure 5.4 shows SCR amplitude, magnitude and latency for JS and controls.

SCR Amplitude: SCR amplitudes (corrected for range) of control subjects were higher compared to JS, $F(1,141) = 20.08$, $p < 0.001$. Analysis of control subjects showed a

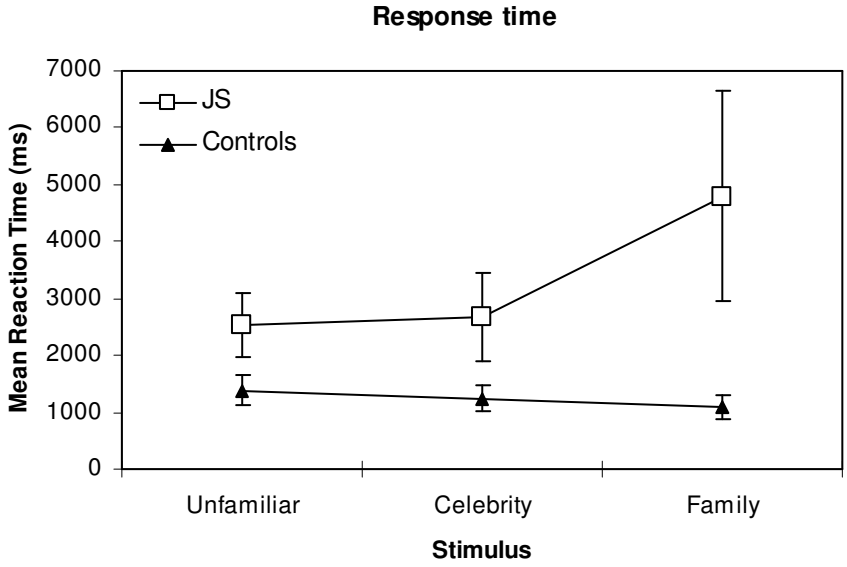


Figure 5.3. Response times of controls and JS to three categories of faces. Error bars show standard deviation

main effect of stimulus type, $F(2,99) = 3.15$, $p < 0.05$. Amplitudes to familiar faces were higher than to unfamiliar faces (Helmert contrast, $p < 0.05$) but there was no difference between amplitudes to celebrities and family. Pairwise Bonferroni comparison showed no significant difference between different types of stimuli.

Analysis of JS' data also showed a main effect of stimulus type on SCR amplitude, $F(1, 42) = 3.72$, $p < 0.05$. Unlike the control subjects, amplitudes to familiar faces were not different from unfamiliar faces. However, amplitudes to family were higher than to celebrities (Helmert contrast, $p < 0.05$). Pairwise Bonferroni comparison showed a significant difference between unfamiliar faces and family ($p < 0.05$).

SCR Magnitude: SCR magnitudes (corrected for range) of control subjects were higher compared to JS, $F(1,174) = 24.19$, $p < 0.001$. Analysis of control subjects' data indicated an effect of stimulus type, $F(2,117) = 6.91$, $p < 0.001$. Amplitudes to familiar faces were higher than to unfamiliar faces (Helmert contrast, $p < 0.05$) but there was no difference between amplitudes to celebrities and family. Pairwise Bonferroni comparison showed a significant difference between unfamiliar faces and family ($p < 0.05$).

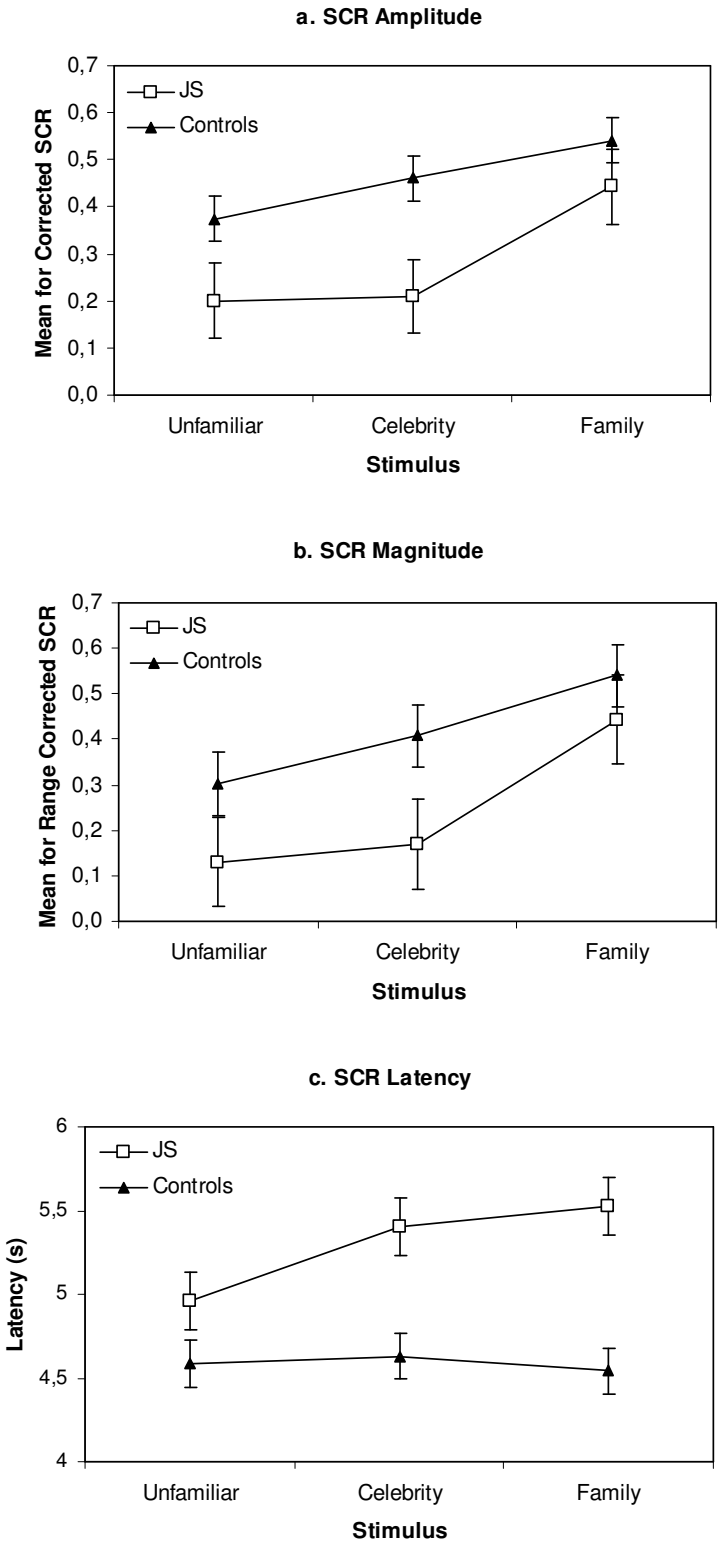


Figure 5.4. Mean SCR Amplitude **(a)**, SCR Magnitude **(b)** and SCR latency **(c)** to presentation of pictures of unfamiliar faces, celebrities and family in the face recognition task. Error bars show standard errors.

Analysis of JS showed a main effect of stimulus type, $F(2,57) = 4.45$, $p < 0.05$. SCR Magnitude to familiar faces was higher than to unfamiliar faces (Helmert contrast, $p < 0.05$), while there was no significant difference between family and celebrities. Post-hoc comparison showed a higher SCR magnitude to family compared to unfamiliar faces ($p < 0.001$)

SCR Latency: SCRs of controls peaked earlier than SCRs of JS, $F(1,174) = 68.33$, $p < 0.001$. Analysis of control subjects showed no significant effect of stimulus type. $F(2,117) = 0.29$, n.s. Analysis of JS' SCR latencies showed a main effect of stimulus type, $F(2.57) = 5.06$, $p < 0.01$. SCR peaks to familiar faces had longer latencies than to unfamiliar faces (Helmert contrast, $p < 0.01$), while latencies to celebrities and family did not differ significantly. Post-hoc comparison showed that latencies to family were longer than to unfamiliar faces ($p < 0.05$).

5.4 Discussion

In this study, we described a patient JS who displayed some characteristics of both prosopagnosia and Capgras delusion. Unlike previously described patients with Capgras delusion, but similar to prosopagnosia, JS has impaired recognition of previously familiar faces. However, she is far less accurate at recognizing close family members compared to celebrities and also has disproportionately longer response times to faces of family than to faces of celebrities. Moreover, JS' perceptual problem is not just a matter of poor recognition by itself: a delusional attribution plays part in her believe that some of her close family members appear strange or repulsive. Like previously reported patients with Capgras delusion (Ellis et al., 1997; Ellis et al., 2000; Hirstein & Ramachandran, 1997), JS' SCRs to familiar faces are lower than that of controls. Nevertheless, SCRs to faces of family members were much higher than to unfamiliar faces.

5.4.1 Selective prosopagnosia

Explaining JS' disorder as a form of prosopagnosia in terms of the adapted model of Bruce and Young (1986) as proposed by Ellis and Lewis (2001), would implicate a disconnection between FRUs and PINs (see Figure 5.1). According to the model, the increased SCRs to faces of family would indicate that covert face recognition of

family members via the affective route is still intact. However, the model does not provide a straightforward explanation why JS is more impaired at recognizing family members than at recognizing celebrities. One explanation might be that the PINs for family members are more impaired than the PINs for celebrities. This however would imply that family PINs and celebrity PINs are stored in different locations in the brain. If this were to be the case, then selective impairments of specific categories of faces would perhaps be more common. To our knowledge, selective prosopagnosia for a specific category of faces has not been reported before.

Discrepancies between impaired overt and preserved covert face recognition may also be interpreted in terms of a disconnection between intact 'early' visual processing and later processes related to conscious awareness (De Haan et al., 1992; Tranel & Damasio, 1988). This disconnection would then prevent overt recognition of faces, while measures of covert processing only reflect the early stages of processing. However, in case of JS, this would imply a selective disruption of those connections involved in recognition of close family members. JS has some small but distinct deep white matter lesions in the left medial temporal lobe. Perhaps these lesions selectively impaired recognition of family members, while leaving recognition of other people relatively intact.

5.4.2 Prosopagnosia paired with delusional beliefs

According to the adapted model of Bruce and Young (Bruce & Young, 1986; Ellis & Lewis, 2001), the delusional beliefs that are the hallmark of Capgras are thought to be the result of a discrepancy between intact overt and impaired covert recognition. The delusional attribution that a significant other is replaced by an impostor, is thought to be the result of this discrepancy. However, prosopagnosia patients do not have such a delusional attribution, even though there is a discrepancy between impaired overt and intact covert recognition. Also, some patients with damage to ventromedial regions of frontal cortex may show a reduced SCR to familiar faces as well, but these patients are not delusional (Tranel et al., 1995). Therefore, a discrepancy between intact overt and impaired covert processing is thought not to be sufficient to develop Capgras delusion (Breen et al., 2000a; Langdon & Coltheart, 2000). Capgras delusion is thought to be the result of two neuropsychological impairments. The first impairment provides the patient with the inconsistent perceptual information and is the root of the delusional believe, while a second neuropsychological impairment prevents the

patient from dismissing this believe as improbable (Coltheart, 2005; Fine et al., 2005; Hirstein & Ramachandran, 1997).

Assuming that JS' SCRs reflect preserved covert face recognition, the inconsistency between covert and overt processing is the reverse as the one seen in Capgras delusion, namely intact covert and impaired overt recognition. JS' impaired overt recognition of familiar faces can be related to her temporal lobe damage. The delusional believe that people looked strange or unattractive might have resulted from a combination of this temporal lobe damage with an older lesion in the right frontal lobe. Along this line of reasoning, the temporal lobe damage caused (moderately) impaired overt face recognition, while the frontal damage gave rise to the attribution that familiar people somehow looked different. The delusional attribution thus might 'explain' the discrepancy between absent overt recognition of family members and the intact feeling of familiarity by assuming that the appearance of family members must have changed. Overt face recognition might be equally impaired for family and celebrities, but as the discrepancy between the intact covert recognition and impaired overt recognition would be more significant for family members (and other people with a strong emotional connotation, such as Adolph Hitler), JS would be more inclined to report that she does not recognize her family.

5.4.3 Variant of Capgras delusion

It could also be considered that JS' condition is a variety of Capgras delusion. In that case, JS has a mild or different form of Capgras delusion, in which the belief that close relatives have been replaced by look-alikes is weakened to a less implausible delusion. The attribution process underlying JS' delusion might be that, since the feeling of familiarity is missing, seeing different (slightly repulsive) looks are 'necessary' to explain the lack of experienced emotional attachment.

However, earlier studies of Capgras delusion showed completely absent autonomic responses to familiar faces (Ellis et al., 1997; Ellis et al., 2000; Hirstein & Ramachandran, 1997), whereas JS showed increased SCRs to faces of family compared to unfamiliar faces. If JS has a mild form of Capgras delusion, then her higher SCRs to family members cannot be explained by the current model (Ellis & Lewis, 2001). It could yet be possible that the SCRs are not as exclusively linked with the affective response to familiar stimuli as the model suggests. One possibility might be that the SCRs are an indirect reflection of the emotional arousal that is generated

by the delusional attribution process, rather than a direct index of covert recognition. In support of this notion, JS has a somewhat different pattern of SCRs than control subjects. First, JS had longer SCR latencies compared to controls. Second, in control subjects, the important contrast explaining differences in SCR amplitudes was between familiar (i.e. family and celebrities) and unfamiliar faces. In JS, the significant contrast was not between familiar and unfamiliar faces, but between family members and celebrities. These differences in SCR pattern might indicate that the SCRs in controls reflect a different mechanism than the SCRs in JS. In terms of the model, this would imply that apart from a direct link between the covert route for face recognition and the SCR, there may also be a link between the attribution processes and the SCR.

Notably, one of the highest SCR amplitudes recorded in our controls occurred during a trial in which the wrong response ('no') was given after presentation of a close family member (the subjects' husband). In that particular case, the control was aware of her mistake and this probably gave rise to emotional arousal. A comparable process might have occurred in JS when seeing photos of family members, as she experienced incongruence between the explicit recognition of a familiar face and her attribution that it was an unfamiliar face.

Another explanation for the increased SCR amplitudes to familiar faces might be that indeed SCRs are indicative of some form of covert recognition as a result of an orienting response to faces of family members, as is suggested by the model, but that this is not the same as 'feeling' that someone is familiar.

5.4.4 Concluding remarks

Whether JS' disorder of face recognition is more related to Capgras delusion or to prosopagnosia, to the best of our knowledge, a disproportionate impairment in recognition of close family members compared to celebrities has not been reported before. Our findings provide evidence that, at least to a certain extent, different mechanisms may underlie recognition of close family members compared to celebrities. This suggestion has also been made by Gobbini et al., who found that different brain regions are involved in response to faces of friends and family compared to faces of celebrities (Gobbini & Haxby, 2004).

Acknowledgements

The authors would like to thank dr. B.M. de Jong for his help with the interpretation of the CT and MRI data.

References

Barton, J. J., Cherkasova, M. V., & Hefter, R. (2004). The covert priming effect of faces in prosopagnosia. *Neurology, 63,* 2062-2068.

Bauer, R. M. (1984). Autonomic recognition of names and faces in prosopagnosia: a neuropsychological application of the Guilty Knowledge Test. *Neuropsychologia, 22,* 457-469.

Bourget, D. & Whitehurst, L. (2004). Capgras syndrome: a review of the neurophysiological correlates and presenting clinical features in cases involving physical violence. *Canadian Journal of Psychiatry, 49,* 719-725.

Breen, N., Caine, D., Coltheart, M., Hendy, J., & Roberts, C. (2000a). Towards an understanding of delusions of misidentification: Four case studies. *Mind and Language, 15,* 74-110.

Breen, N., Caine, D., & Coltheart, M. (2000b). Models of face recognition and delusional misidentification: A critical review. *Cognitive Neuropsychology, 17,* 55-71.

Bruce, V. & Young, A. (1986). Understanding face recognition. *British Journal of Psychology, 77 (Pt 3),* 305-327.

Coltheart, M. (2005). Conscious experience and delusional belief. *Philosophy, Psychiatry & Psychology, 12,* 153-156.

Damasio, A. R. (1985). Prosopagnosia. *Trends in Neurosciences, 8,* 132-135.

Damasio, A. R., Damasio, H., & Vanhoesen, G. W. (1982). Prosopagnosia - Anatomic Basis and Behavioral Mechanisms. *Neurology, 32,* 331-341.

De Haan, E. H. F., Bauer, R. M., & Greve, K. W. (1992). Behavioural and physiological evidence for covert face recognition in a prosopagnosic patient. *Cortex, 28,* 77-95.

De Haan, E. H. F., Young, A., & Newcombe, F. (1987). Face Recognition Without Awareness. *Cognitive Neuropsychology, 4,* 385-415.

De Haan, E. H. F., Young, A. W., & Newcombe, F. (1991). Covert and overt recognition in prosopagnosia. *Brain, 114 (Pt 6),* 2575-2591.

DeRenzi, E., Perani, D., Carlesimo, G. A., Silveri, M. C., & Fazio, F. (1994). Prosopagnosia can be associated with damage confined to the right hemisphere--an MRI and PET study and a review of the literature. *Neuropsychologia, 32,* 893-902.

Ellis, H. D. & Lewis, M. B. (2001). Capgras delusion: a window on face recognition. *Trends in Cognitive Sciences, 5,* 149-156.

Ellis, H. D., Lewis, M. B., Moselhy, H. F., & Young, A. W. (2000). Automatic without autonomic responses to familiar faces: Differential components of covert face recognition in a case of Capgras delusion. *Cognitive Neuropsychiatry, 5,* 255-269.

Ellis, H. D. & Young, A. W. (1990). Accounting for delusional misidentifications. *British ournal of.Psychiatry, 157,* 239-248.

Ellis, H. D., Young, A. W., Quayle, A. H., & De Pauw, K. W. (1997). Reduced autonomic responses to faces in Capgras delusion. *Proc.Biol.Sci., 264,* 1085-1092.

Fine, C., Craigie, J., & Gold, I. (2005). Damned if you do, damned if you don't; the impasse in cognitive accounts of the Capgras delusion. *Philosophy, Psychiatry & Psychology, 12,* 143-151.

Gobbini, M. I. & Haxby, J. V. (2004). Person knowledge and emotion in the neural representation of faces. *International Journal of Psychophysiology, 54,* 26.

Hirstein, W. & Ramachandran, V. S. (1997). Capgras syndrome: a novel probe for understanding the neural representation of the identity and familiarity of persons. *Proceedings of the Royal Society B: Biological Sciences, 264,* 437-444.

Langdon, R. & Coltheart, M. (2000). The cognitive neuropsychology of delusions. *Mind and Language, 15,* 184-218.

Tranel, D. & Damasio, A. R. (1988). Non-conscious face recognition in patients with face agnosia. *Behavioural Brain Research, 30,* 235-249.

Tranel, D., Damasio, H., & Damasio, A. R. (1995). Double Dissociation Between Overt and Covert Face Recognition. *Journal of Cognitive Neuroscience, 7,* 425-432.

Young, A. W., Hellawell, D., & De Haan, E. H. F. (1988). Cross-Domain Semantic Priming in Normal Subjects and A Prosopagnosic Patient. *Quarterly Journal of Experimental Psychology Section A-Human Experimental Psychology, 40,* 561-580.

Chapter 6

Differential modulations of P1 and N170 in conscious and unconscious processing of emotional faces

Joost Heutink, Wiebo H. Brouwer, Berry Weijers, Norbert Börger & Anke Bouma

Abstract

The present study was designed to investigate the early processing of conditioned angry faces (CS+), unconditioned angry faces (CS-) and neutral faces (N) in 32 young adults. We assessed Event-Related Potentials (ERPs) to conscious and unconscious processing of facial stimuli, while controlling for self-reported state and trait anxiety scores (STAI). P1 and N170 amplitudes were modulated differentially, dependent on the level of awareness of face stimuli. Under conditions of subliminal presentation, P1 appeared sensitive to both the effects of basic emotional expression of faces (N v CS-) and classical conditioning (CS+ v CS-). Under conditions of subliminal presentation, N170 was only sensitive for effects of classical conditioning, while under supraliminal presentation N170 was only sensitive for basic emotional expression. Moreover, under conditions of subliminal presentation, trait anxiety had an effect on P1 in the right hemisphere, with a specific interaction between trait anxiety and type of face stimuli. State anxiety on the other hand, had an effect on N170 amplitudes in the left hemisphere under conditions of both subliminal and supraliminal presentation of face stimuli. The present results suggest that P1 amplitude to emotional face stimuli is mainly influenced by re-entrant projections of the amygdala to the cortical stream. The results further suggest that N170 reflects primarily cortical processes, however, conscious and subconscious processing of face stimuli can differentially modulate these processes.

6.1 Introduction

6.1.1 Emotional processing and the amygdala

Emotional processing, and in particular processing of facial emotional expressions, plays a crucial role in the evolutional survival and adaptation of the human species (LeDoux, 1996). Given the biological and social relevance of emotional expressions, recognition of and response to facial expressions must be both quick and accurate to allow rapid, appropriate responses. It has been argued that subcortical brain structures are continuously involved in the automatic and pre-attentive processing of emotional relevant (e.g. threatening) cues, thus allowing rapid ('instinctive') behavioural responses on one hand, and prioritising enhanced, higher order attentive processing of these cues on the other hand (LeDoux, 1996; LeDoux, 2000).

The amygdalae, located bilaterally within the medial temporal lobes, are thought to play a pivotal role in at least two semi-independent, yet interacting pathways that underlie the recognition of emotional signals in the visual domain (Adolphs, 2002; LeDoux, 2000; Zald, 2003). As well as receiving elaborate input from cortical areas such as the anterior temporal lobes (Amaral et al., 1992) and the prefrontal cortex (Davidson & Irwin, 1999), studies in animals and in humans suggest that the amygdalae may also receive crude sensory information directly from the superior colliculus and the pulvinar thalamus, bypassing the striate and extrastriate cortex (Doron & LeDoux, 1999; Mazurski et al., 1996; Morris et al., 2001). Input via the colliculi-pulvinar-amygdala pathway would allow extremely fast responses to biologically and socially relevant stimuli, outside the scope of human consciousness (LeDoux, 1996; Morris et al., 2001; Whalen et al., 1998). Different types of emotional stimuli have been suggested to qualify for this thalamo-amygdalar processing without cortical involvement. These include emotional facial expressions (Adolphs et al., 1994; Morris et al., 1996; Vuilleumier et al., 2002) and aversively conditioned stimuli (Doron & LeDoux, 1999; LeDoux et al., 1984; Morris et al., 1998b). Thalamo-amygdalar processing of these classes of stimuli without cortical involvement may have the crucial advantage of priming sensory systems pre-attentively (Armony & Dolan, 2002; Davidson & Irwin, 1999; Zald, 2003), thus facilitating the precise identification of the stimulus by the cortical pathway. Evidence for such emotion-dependent modulation of the sensory cortex has been provided by imaging studies,

which showed that activity in the extrastriate brain regions is functionally correlated with amygdala activation (Morris et al., 1998a; Morris et al., 1999).

There is some evidence of asymmetry in amygdala responses to emotional stimuli. In one particular PET study (Morris et al., 1998b), subjects were presented photographs of neutral faces and two angry faces. Prior to the experiment, one of the angry faces had been associated with an aversive noise using classical conditioning principles. The other angry face was never paired with the aversive noise. Backward masking with neutral faces in half of the presentations allowed stimuli to be presented either subliminally (masked) or supraliminally (unmasked). It was found that the masked conditioned angry face elicited right amygdala activation, whereas the unmasked conditioned angry face was correlated with left amygdala activation. Unfortunately, the low temporal resolution of PET makes it hard to tell from this particular study whether cortical input to the amygdala contributed to the effects or not or whether the amygdala received its input directly from the pulvinar and superior colliculus.

6.1.2 ERPs and processing of facial expressions

Although event-related brain potentials (ERPs) do not allow direct assessment of subcortical visual processing, ERP studies do have the crucial advantage of excellent temporal resolution compared to PET and fMRI, thus potentially providing greater understanding of the mechanisms underlying both pre-attentive emotional processing and the timeframe of the different stages of decoding of facial expressions.

According to Bruce and Young's influential model, processing of more complex facial information such as facial identity and emotional expression is preceded by a stage of structural encoding during which facial features and configurations are integrated to generate a face representation (Bruce & Young, 1986). In ERP literature, the phase of structural encoding has been linked with the N170, culminating at posterior electrode positions (Bentin et al., 1996; Eimer, 1998; Eimer, 2000b; Eimer & McCarthy, 1999; Sagiv & Bentin, 2001). The N170 is thought to be a face-specific component as N170 amplitudes are most often larger in response to faces than to other objects (Bentin et al., 1996; Eimer, 1998; Sagiv & Bentin, 2001).

In support of the assumption that emotional recognition and identification of faces occur after this initial stage of structural encoding, reflecting the operation of

detecting faces rather than identifying them, some studies have provided evidence that the N170 is not influenced by emotional expression (Eimer & Holmes, 2002; Holmes et al., 2003) or familiarity of faces (Bentin & Deouell, 2000; Eimer, 2000a). There is some evidence however, that face-selective processing may occur before the N170. The P1, which is frequently regarded as the earliest endogenous ERP component in visual processing (Hopf & Mangun, 2000; Martinez et al., 2001) and linked with extrastriate activity (Foxe & Simpson, 2002; Heinze et al., 1994), has been shown to be sensitive to faces as well. For instance, larger P1 amplitudes have been found for inverted faces compared to upright faces (Linkenkaer-Hansen et al., 1998) and for unattractive and atypical faces compared to prototypical faces (Halit et al., 2000), indicating that face-selective activity can already occur well before the N170. In a MEG study, it was demonstrated that M100 amplitudes were higher for faces than non-faces and correlated with the categorization of faces, while the M170 was correlated with the categorization and identification of faces (Liu et al., 2002).

Further, several studies showed that facial emotional expression may affect earlier stages of facial processing than the N170. Eimer and Holmes (2002) found that fearful faces elicited a frontocentral activity around 120 ms after stimulus presentation and in a MEG study, Streit et al. (1999) found that activations related to emotional content of faces already started 160 ms after stimulus onset in the right temporal cortex and the inferior occipital cortex. Using dichoptic presentation of schematic line drawings of faces, Eger et al. (2003) found an effect of emotional expression 85 ms after stimulus presentation, while Pizzagalli et al. (1999) found an effect of liked versus disliked faces at this early stage of processing. In another study, early ERPs to six basic emotional expressions were investigated (Batty & Taylor, 2003). P1 latency did not vary with emotional expression, but there was an effect of emotion on P1 amplitude, with neutral and surprised faces producing the smallest P1 amplitudes. Nevertheless, post-hoc analysis did not reveal differences between any two emotions.

To summarize, several ERP studies have provided evidence that some encoding processes of facial configuration may occur before the structural encoding of a face takes place, especially when these encoding processes are emotion-dependent. It could be argued that the emotion-dependent modulation of the early ERP components reflects re-entrant projections from the amygdala to the visual cortex, relying on input from the thalamic sensory relay (Mazurski et al., 1996), which prime the visual cortex to gain preferential access to recognition of visual stimuli

(Heinze et al., 1994), thus facilitating a quick response to emotionally significant stimuli (Batty & Taylor, 2003; Pizzagalli et al., 1999).

6.1.3 Current Study and Hypotheses

In the present study, we wanted to take a further step in bridging the gap between the imaging studies that established facial expression-dependent modulation of amygdala activation and ERP studies that showed that emotion-dependent processing of facial stimuli can take place before structural encoding. To this end, we aimed to extend these earlier ERP findings in several ways.

Firstly, we compared processing of three types of facial stimuli, namely neutral expression (N), unconditioned angry expression (CS-) and aversely conditioned angry expression (CS+). This comparison would allow us to investigate the effect of basic emotional expression on early facial processing on one hand, and the effect of classical conditioning on the other hand. These three classes of stimuli allow two relevant comparisons of early ERPs. The differences between N and CS- can be attributed to differences in basic emotional expression of the faces, whereas differences between CS+ and CS- reflect the effects of aversive-conditioning processing. Moreover, since the CS+ and CS- stimuli have the same emotional expression, a difference in early ERPs between these two stimuli would also indicate within-category discrimination of faces based on encoding of other facial features than expression alone.

Secondly, we compared unconscious, covert, processing of these stimuli with conscious, overt, processing by using a backward masking technique. Backward masking is based on the principle that the perceptual consolidation of a first stimulus (a target) is interrupted by a second stimulus (a mask) which is presented shortly after the target, thus preventing conscious identification of the target (Di Lollo et al., 2000; Enns & Di Lollo, 2000). It has been suggested that the human amygdala is particularly sensitive to unconscious processing of subliminally presented facial expressions (Morris et al., 1998b; Morris et al., 1999; Whalen et al., 1998), though this effect may be limited to the basolateral subregion of the amygdala (Etkin et al., 2004). If emotion-dependent modulation of early visual ERPs reflects projections of the amygdala to the visual cortex -as had been previously suggested- a difference between conscious and unconscious processing of the same classes of facial stimuli might provide further evidence for this hypothesis.

Thirdly, increased amygdala activation has been well-established in imaging studies comparing clinical populations such as social phobia (Birbaumer et al., 1998; Stein et al., 2002), post-traumatic stress disorder (Rauch et al., 2000) and depression (Sheline et al., 2001) to controls. Assuming that early visual ERPs to emotional stimuli may at least partly reflect re-entrant projections of the amygdala to the visual cortex, we wanted to control for a possible relationship between our subjects' experienced anxiety in everyday life and early emotional processing. Differences in experienced anxiety were obtained via the quantitative state and trait measures in Spielberger's State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1970)

Fourthly, since requiring subjects to explicitly label facial emotional expressions may result in deactivation of the amygdala (Hariri et al., 2000), we asked subjects to judge the age of the faces presented. Judgement of the facial emotional expression of the stimuli was not required for the task.

As we were particularly interested in the early effects of emotional visual processing on ERPs, we focused our analysis on the period of time from stimulus onset until structural encoding (0-250 ms).

6.2 Methods

6.2.1 Subjects

Thirty-two healthy right-handed graduate students (16 male, mean age 21.4 yr., *SD* 2.2 and 16 female, mean age 21.5 yr., *SD* 2.1) were paid €11.50 for participation. All subjects had normal or corrected-to-normal vision. Psychology students were excluded from the study since their knowledge about classical conditioning principles might interfere with the objectives of the experiment. Instructions were provided via mail and all subjects gave written consent prior to participation. Participants were asked not to drink alcohol on the day before the experiment and not to drink any coffee on the day of the experiment. All subjects were naive with respect to the specific questions investigated but were debriefed and informed about the purpose of the experiment immediately after the experiment took place. The experiment was conducted in accordance with the ethical standards laid down in the 1964 declaration of Helsinki.

6.2.2 Stimulus material

The stimuli consisted of eleven digital greyscale photographs of different faces from Ekman and Friesen's 'pictures of facial affect' (Ekman & Friesen, 1976). Nine faces had a neutral expression and two faces had an angry expression. All pictures were modified is such a way that features in the outer contours, such as neck and hair were made black and that all stimuli had similar size and luminance.

6.2.3 Procedure

Experiments were conducted in a Faraday chamber. All stimuli were presented in the centre of a 17 inch monitor (resolution 800 x 600, refresh rate 16.7 ms) at 70 cm viewing distance (6,5° visual angle).

In six conditioning blocks, each preceding an experimental block, subjects were presented a sequence of 50 trials. Each trial consisted of the following sequence (Figure 6.1a): a warning cue '*' (300 ms) in the centre of the screen, followed by a black screen (400-600 ms), a greyscale image of a face (1000 ms), a black screen (1000 ms), and a response cue '?' (1000 ms), followed by another black screen (2000 ms). Half of the facial stimuli consisted of the nine neutral faces (N), the other half consisted of one of the angry faces. Fifty percent (i.e. alternately 12 or 13 out of 25) of the presentations of the angry face (CS+) were accompanied by a 90 dB white noise burst of 100 ms (Figure 6.1b).

In the six experimental blocks, which each followed a conditioning block, an unconditioned angry face (CS-) was added to the set of presented stimuli. In each experimental block, subjects viewed a sequence of 60 trials, but now each trial consisted of a pair of faces, namely a subliminally presented target followed by a supraliminally presented mask. In the experimental blocks, the CS+ was never paired with the white noise burst. Each trial consisted of the following sequence (Figure 6.2): a warning cue '*' (300 ms) in the centre of the screen, followed by a black screen (400-600 ms), the target (16.7 ms), a black screen (16.7 ms), the mask (1000 ms), a black screen (1000 ms), and a response cue '?' (1000 ms), followed by another black screen (1960 ms).

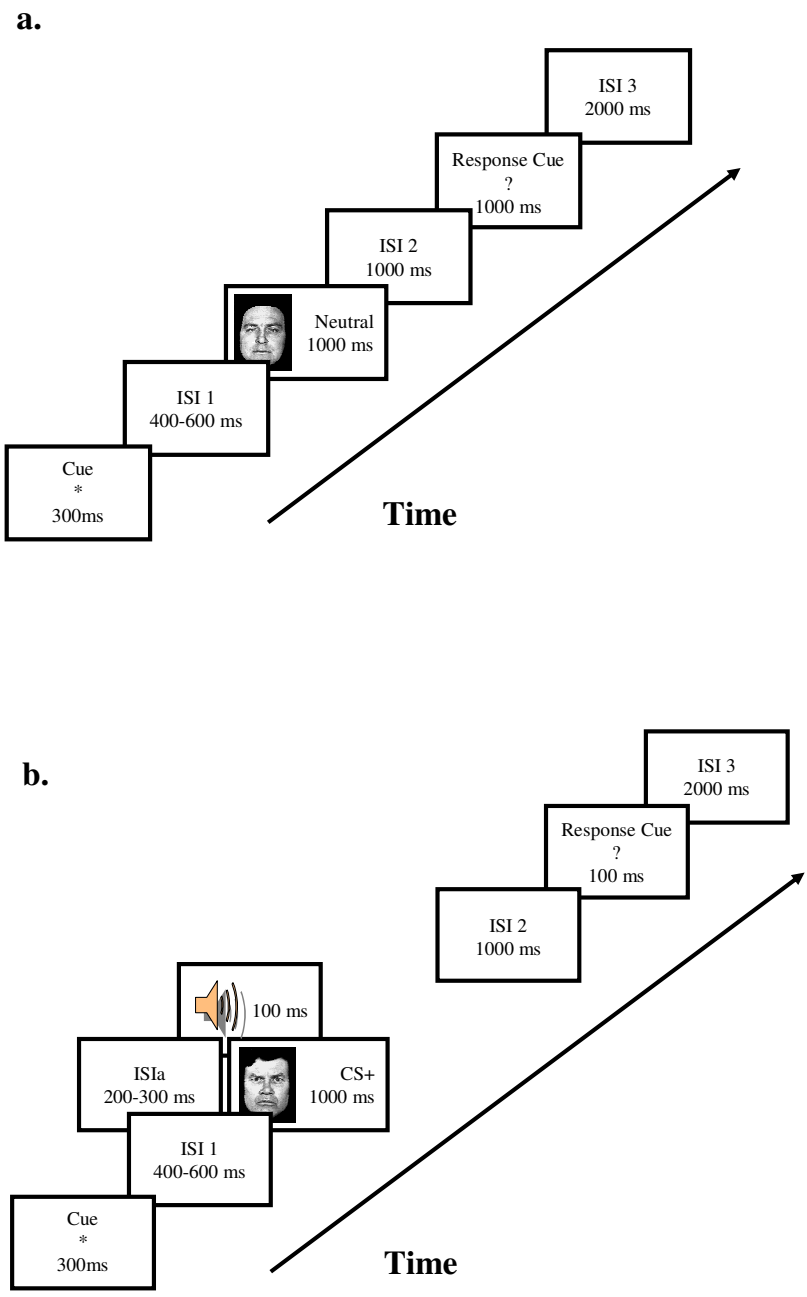


Figure 6.1. Schematic outline of the conditioning block; **(a)** presentation of a trial with a neutral face; **(b)** a trial with an angry face, which was coupled with a 90dB white noise burst in 50% of presentations.

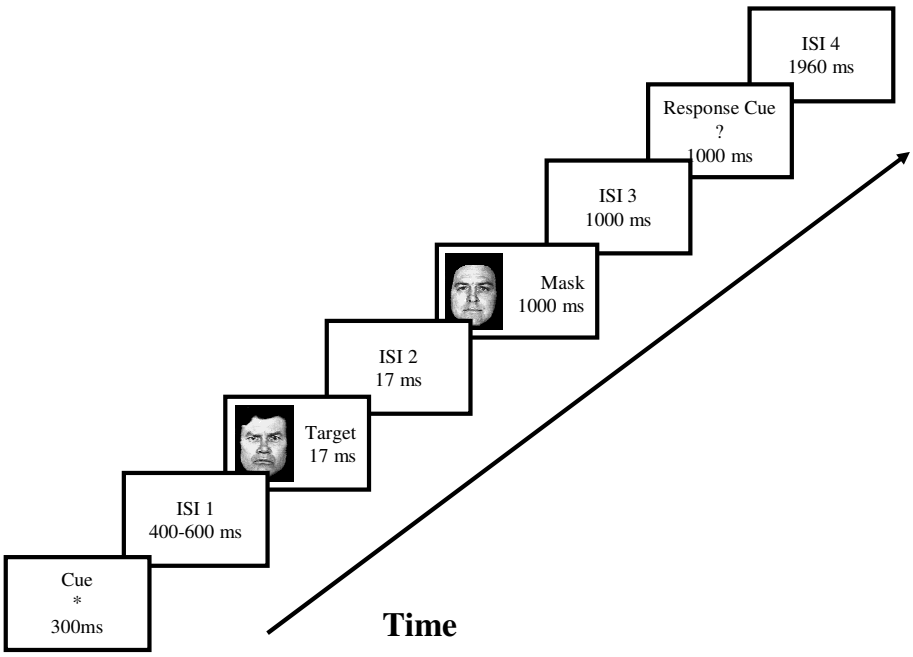


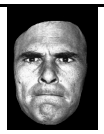
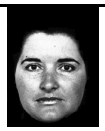
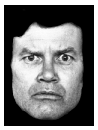
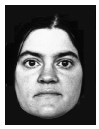
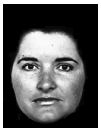
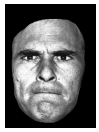
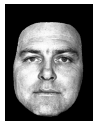
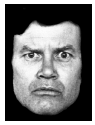
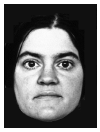
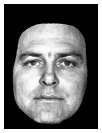
Figure 6.2. Schematic outline of a single trial in the experimental blocks, consisting of a subliminally presented target and a supraliminally presented mask. During experimental blocks, CS+ was never paired with the white noise burst.

The 16.7 ms black screen between the presentation of the target and the mask was added to prevent the possibility that the target-mask sequence might be perceived as the presentation of a single face with a quickly changing expression. The backward masking sequence was piloted in 6 additional subjects prior to the experiment, to ensure that the target could not be recognized. In this procedure, each subject was presented with 100 masked imaged of faces (50 neutral, 50 angry). None of the subjects was able to label these emotions (neutral or angry) above chance level. Also, in another experiment, the same paradigm was used in 3 subjects, who were asked to label 180 masked images of unfamiliar faces and familiar faces (family and celebrities). Judgements (familiar or unfamiliar) of theses subjects were not significantly above chance level. As an additional control, all subjects who participated in the experiment were asked how they had perceived the target-mask sequence. Most subjects had been aware of a brief 'flash' before the face was presented, but only two subjects suspected that these 'flashes' might have been

images of faces. These two subjects also reported that they had not been able to distinguish any features of the masked faces; neither had they been able tell the emotional expression or sex of the images.

In each experimental block, five different conditions were presented in pseudo-random order (Table 6.1): (*1*) subliminal CS+, in which the CS+ angry face (previously paired with white noise) was the target and a neutral face was the mask; (*2*) subliminal CS-, in which the CS- angry face (not paired with white noise) was the target and a neutral face was the mask; (*3*) supraliminal CS+, in which a neutral face was the masked target and the CS+ the mask; (*4*) supraliminal CS-, in which a neutral face was the masked target and the CS- the mask; (*5*) supraliminal neutral face, in which both the subliminal target and the supraliminal mask consisted of a neutral face.

Table 6.1. Five types of conditions presented in the experimental task. Each subliminally presented Target stimulus was followed by a Mask. Subjects only perceived a brief flash prior to the mask and were unaware of the identity or emotional expression of the target.

Condition	Target (17 ms)		Mask (1000 ms)	
1.	CS+		Neutral	
2.	CS-		Neutral	
3.	Neutral		CS+	
4.	Neutral		CS-	
5.	Neutral		Neutral	

Each of the five conditions was presented 12 times in every experimental block. In both the conditioning blocks and the experimental blocks, subjects were asked to press a foot-pedal if the presented face met certain criteria, which changed every new conditioning block. Subjects were told that the conditioning block was merely a practice for the 'real' experimental blocks and were told not to be distracted by the loud noises that were administered via the headphone. The task did not require emotional evaluation of the faces and none of the given instructions were related to the differences in emotional expression between the faces. The consecutive instructions were: "press the foot pedal with your right foot if you think the picture is of a woman older than 50 years" (conditioning block 1 and experimental block 1); "press your left foot for a man older than 55" (blocks 2); "press your right foot for a woman younger than 25" (blocks 3); "press you left foot for a woman older than 50" (blocks 4); "press your right foot for a man older than 55" (blocks 5); "press your left foot for a woman younger than 25" (blocks 6). These instructions were chosen in such a way that a maximum of 6 responses were required in each block. Unspeeded responses were given by the subjects when the response cue ('?') appeared on the screen.

The identity of the CS+ and CS- faces was balanced across subjects: for half of both female and male subjects angry face A acted as CS+ and angry face B as CS-, while for the remaining subjects angry face B acted as CS+ and angry face A was CS-. The five different stimulus conditions were presented randomly in each experimental block, with the following restrictions: the same stimulus condition was never presented two times in succession and the same face was not presented twice in a single target-mask combination.

Immediately before the experiment (after the instruction), all subjects completed the State and Trait versions of the STAI (Spielberger et al., 1970) (Dutch translation: Hermans (1994)).

6.2.4 Electrophysiological recordings

EEG data were recorded from 15 electrodes corresponding to the traditional 10/20 system: Fp1, Fp2, F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, T3, T4, O1 and O2 with the right mastoid as reference. A standard electrodecap (ElectroCap) with Tn electrodes was used to apply the electrodes. Combined horizontal and vertical EOG was measured by Ag/AgCl electrodes placed above the left eye and on the outer canthus of

the right eye. Impedance was kept below 5 kΩ. EOG and EEG were amplified with a 10 s time constant and a 200 Hz low pass filter, sampled at 1000 Hz, digitally filtered with a 30 Hz lowpass Hamming filter and on-line reduced to a sample frequency of 200 Hz. ERPs were averaged off-line using BrainVision© software, automatically rejecting trials with EEG artefacts (activity above 195 μV or below -195μV), while contribution of eye movements and blinks was corrected (Gratton et al., 1983). A baseline voltage of 100 ms preceding stimulus onset was taken. For all ERPs, the start of the presentation of the subliminally presented target was time zero for averaging.

6.2.5 Conscious and unconscious perception

As can be derived from Table 6.1, the five stimulus conditions were chosen in such a way that each sequence consisted of at least one Neutral face, either preceded or followed by a CS+, a CS- or another Neutral face. This would allow us to compare the differences between the three classes of stimuli under conditions of subliminal presentation or supraliminal presentation. In the analysis for subliminal presentation, the three stimulus conditions with a neutral mask were compared (condition 1, 2 and 5). In these three conditions, the subliminally presented CS+, CS- and Neutral target stimuli are all followed by a Neutral mask. Any effect that is found as a result of this comparison can therefore be attributed to the differences between the subliminally presented (i.e. unconsciously perceived) stimuli.

In the analysis for supraliminal presentation, the three stimulus conditions with a neutral target but with different masks were compared (condition 3, 4 and 5). In this comparison, the crucial difference between the stimuli is the type of mask: CS+, CS- or Neutral. As all masks are preceded by a Neutral target stimulus, effects that are found in this comparison are the result of differences between supraliminally presented (i.e. consciously perceived) stimuli.

6.2.6 Data analysis

After visual inspection of the data, peak latencies and mean amplitudes were calculated per subject, experimental block and electrode position, using BrainVision© semi-automatic peak detection. All data were analysed with SPSS 11.01 for Windows. Separate analyses were performed for subliminal and supraliminal presentation.

Each analysis consisted of a general linear model (GLM) repeated measures (RM) analysis of variance (ANOVA) with the factors stimulus type (3 levels: N, CS-

and CS+), laterality (2 levels: left and right hemisphere) and experimental block (6 levels). In cases where the assumption of sphericity was violated, Greenhouse-Geisser correction for degrees of freedom was used. Tests of within-subject contrasts were performed for the Neutral v CS- stimuli and the CS+ v CS- stimuli. Bonferroni correction for multiple comparisons was used for post-hoc analysis of effects. An additional analysis consisted of a GLM RM ANOVA (factors: stimulus type x laterality x experimental block) with STAI state and STAI trait score as covariates and sex as between-subject factor.

6.3 Results

6.3.1 Behavioural data

None of the subjects' scores on the STAI Trait version (M = 34.1, SD = 8.1) or State version (M = 32.0, SD = 6.7) fell within pathological range. T-tests showed no significant differences between STAI State or STAI Trait scores of male and female subjects. Trait and State scores did not correlate significantly, (Pearson) $r(30) = .32$, $p > 0.05$ (n.s.).

6.3.2 Electrophysiological data

Visual inspection of the data resulted in two peaks being analysed: an early positive peak, ranging from 130-150 ms (P1) after the onset of the first stimulus and culminating at the occipital electrodes, and a negativity ranging from 190-200 ms (N170) after stimulus onset, and also culminating at the occipital electrodes O1 and O2. At more anterior electrodes, no other peaks were found within the aforementioned timeframe (0-250 ms). The results of the data analysis are summarized in Table 6.2.

6.3.2.1 Subliminal presentation / Unconscious perception

<u>P1 amplitudes:</u> GLM RM (factors: stimulus type x laterality x experimental block) showed a significant effect of stimulus type ($F(2,62) = 19.59$, $p < 0.001$) and a significant stimulus type x laterality interaction ($F(2,62) = 18.34$, $p < 0.001$). To investigate this stimulus type x laterality interaction, O1 and O2 were analysed separately.

Table 6.2. Summary of results of early ERP components: Effects of type of stimulus (Emotional expression and Conditioning) and subject characteristics (Sex, State anxiety and Trait anxiety) after post-hoc pairwise correction.

	Emotional Expression (N vs. CS-)	Conditioning (CS+ vs. CS-)	Sex	State	Trait	Trait x Stimulus
Subliminal						
O1	P1	P1 & N170	P1	N170		
O2	P1	P1 & N170	P1		P1	P1
Supraliminal						
O1			P1	N170	P1	
O2	N170		P1		P1	

A GLM RM (factors: stimulus type x experimental block) for the left occipital electrode (O1) confirmed the effect of stimulus type ($F(2,62) = 8.18$, $p < 0.01$). Within-subject contrasts showed that this effect was significant for the conditioning effect (i.e. CS+ v CS- comparison) ($F1,31) = 11.33$, $p < 0.01$) as well as for the effect of basic emotional expression (i.e. Neutral v CS- comparison) ($F(1,31) = 8.425$, $p < 0.01$). Post-hoc analysis showed that P1 amplitudes to CS- were higher than to CS+ ($p < 0.01$) and that CS- amplitudes were higher than Neutral amplitudes ($p < 0.05$). Amplitudes for CS+ and Neutral stimuli did not differ significantly (Figure 6.3a).

A GLM RM (factors: stimulus type x experimental block) for the right occipital electrode (O2) showed a significant effect of stimulus type ($F(2,62) = 34.20$, $p < 0.001$). Within-subject contrasts showed that a significant for conditioning ($F(1,31) = 50.25$, $p < 0.001$) and for basic emotional expression ($F(1.31) = 28.05$, $p < 0.001$). Post-hoc analyses showed that P1 amplitudes to CS- were higher than to CS+ ($p < 0.001$) and that CS- amplitudes were higher than Neutral amplitudes ($p < 0.001$). Amplitudes for the CS+ were lower than amplitudes for neutral stimuli ($p < 0.01$) (Figure 6.3b).

P1 latencies: Analysis of the P1 latencies revealed no significant effects for any of the factors.

N170 amplitudes: GLM RM showed a significant effect for stimulus type ($F(2,62) = 15.74$, $p < 0.001$). Within-subject contrasts showed that this effect was only significant for the conditioning contrast ($F(1,31) = 26.49$, $p < 0.001$) but not for the

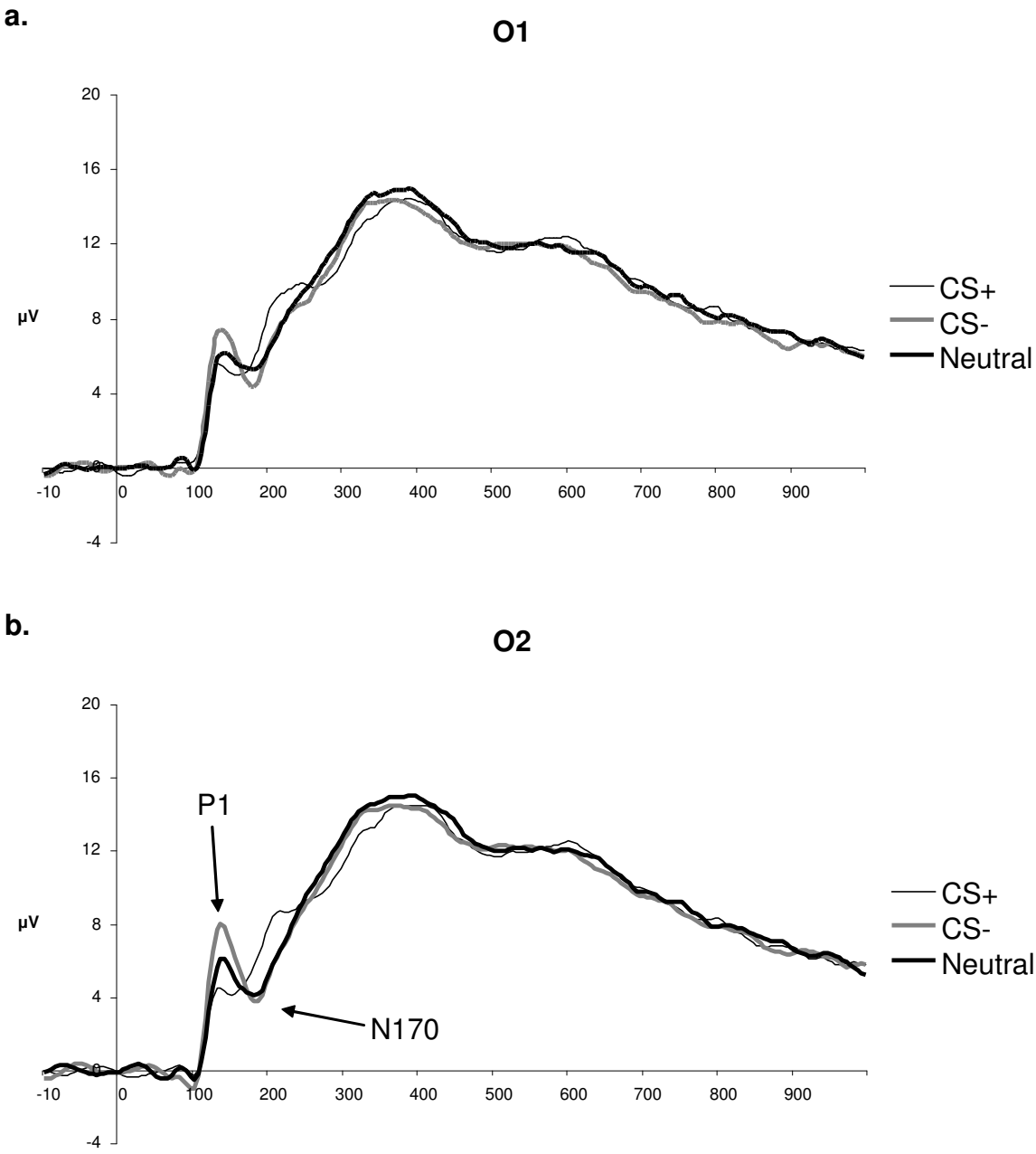


Figure 6.3. Grand averaged ERPs for three subliminally presented face stimuli from the occipital sites O1 and O2.

basic emotional expression contrast. In addition, there was a significant stimulus type x laterality interaction ($F(2,62) = 7.27$, $p < 0.005$) and a significant effect of experimental block ($F(5,155) = 7.64$, $p < 0.001$). Post-hoc pairwise comparisons showed that N170 amplitudes were larger in experimental block 1 as compared to the other blocks (all $p < 0.05$). There were no further significant differences between any

two blocks. To investigate the nature of the stimulus type x laterality interaction, O1 and O2 were analysed separately.

A GLM RM (factors: stimulus type x experimental block) for the left occipital electrode (O1) confirmed the main effects of stimulus type ($F(2,62) = 9.28$, $p < 0.001$) and experimental block ($F(5,155) = 7.46$, $p < 0.001$). The effect of stimulus type was only significant for the conditioning contrast ($F(1,31) = 15.231$, $p < 0.001$) but not for the basic emotional expression contrast. Post-hoc analysis showed that N170 amplitudes to CS+ were weaker than to CS- stimuli ($p < 0.005$) and compared to the Neutral stimuli ($p < 0.005$). Amplitudes for CS- and Neutral stimuli did not differ significantly. Post-hoc pairwise comparisons of the different experimental blocks showed that N170 amplitudes in block 1 were significantly stronger (i.e. more negative) compared to block 3-6 (all $p < 0.05$) but not compared to block 2. There were no further significant differences between any two blocks.

GLM RM (factors: stimulus type x experimental block) for the right occipital electrode (O2) also confirmed the main effects of stimulus type ($F(2.61) = 20.55$, $p < 0.001$) and experimental block ($F(5,155) = 6.78$, $p < 0.001$). Again, the effect of stimulus type was only significant for the conditioning contrast ($F(1,31) = 33.85$, $p < 0.001$), but not for the basic emotional expression contrast. Post-hoc pairwise comparisons showed that N170 amplitudes for CS+ were weaker (i.e. more positive) as compared to CS- ($p < 0.001$) and Neutral stimuli ($p < 0.001$), while CS- and Neutral amplitudes did not differ significantly.

N170 latencies: Analysis of the N170 latencies revealed no significant effects for any of the factors.

6.3.2.2 Supraliminal presentation / Conscious perception

P1 amplitudes: Analysis of the P1 amplitudes revealed no significant effects for any of the factors.

P1 latencies: Analysis of the P1 latencies revealed no significant effects for any of the factors.

N170 amplitudes: A GLM RM showed significant effects for stimulus type ($F(2,62) = 3.30$, $p < 0.05$), laterality ($F(2,62) = 5.349$, $p < 0.05$) and experimental block ($F(5,155) = 5.16$, $p < 0.001$). The effect of stimulus type was only significant for the basic emotional expression contrast ($F(1, 31) = 8.27$, $p < 0.01$), but not for the conditioning contrast. Post-hoc analysis showed stronger (i.e. more negative) N170

amplitudes for Neutral stimuli than for CS- stimuli ($p < 0.05$) but no differences between CS+ and CS- or CS+ and Neutral. The effect of laterality was caused by more negative N170 amplitudes to all stimuli in the right electrode (O2) compared to the left electrode (O1) ($p < 0.05$). Post-hoc pairwise comparisons between the experimental blocks indicated that amplitudes in block 1 were stronger than in blocks 2-6 (all $p < 0.05$), while no differences were found between any of the other blocks. Furthermore, two interactions were found: a stimulus type x laterality interaction ($F(2,62) = 18.2$, $p < 0.001$) and a stimulus type x experimental block interaction (Greenhouse-Geisser corrected for sphericity $F(5.3, 163.6) = 2.33$, $p < 0.05$). The stimulus type x laterality interaction was further investigated by analysing O1 and O2 separately.

For the left occipital electrode (O1) a GLM RM (factors: stimulus type x experimental block) yielded significant effects of experimental block (Greenhouse-Geisser corrected for sphericity $F(3.5, 109.6) = 5.40$, $p < 0.001$) and stimulus type ($F(2,62) = 3.22$, $p < 0.05$). This effect of stimulus type was only significant for the basic emotional expression contrast ($F(1,31) = 4.40$, $p < 0.05$) but not for the conditioning contrast. However, post-hoc pairwise comparisons showed no significant differences between any two stimulus types (Figure 6.4a). Post-hoc analysis of the experimental blocks only yielded a significant difference between block 1 and blocks 2-6 ($p < 0.05$).

For the right occipital electrode (O2) significant effects were found for experimental block ($F(5,155) = 4.93$, $p < 0.001$) and stimulus type ($F(2,62) = 3.82$, $p < 0.05$). Tests for within-subject contrasts showed that the effect of stimulus type was significant for the conditioning contrast ($F(1,31) = 4.36$, $p < 0.05$) as well as the basic emotional expression contrast ($F(1,31) = 9.04$, $p < 0.01$). Post-hoc analysis revealed increased (i.e. more negative) N170 amplitudes for Neutral stimuli compared to CS-, but no further significant differences between CS+ and CS- or CS+ and Neutral stimuli (Figure 6.4b). Post-hoc analysis of the experimental blocks only yielded a significant difference between block 1 and blocks 2-6 ($p < 0.05$).

N170 latencies: GLM RM showed an significant effect of laterality ($F(1,31) = 7.36$, $p < 0.05$): N170 peaks for O1 were slightly later (3.5 ms) than for O2 ($P < 0.05$). A significant effect of stimulus type ($F(2,62) = 5.81$, $p < 0.01$) was also found: N170 peaks for CS+ were slightly later (5.5 ms) than for Neutral ($p < 0.01$), while there were no significant differences between any other two stimulus types.

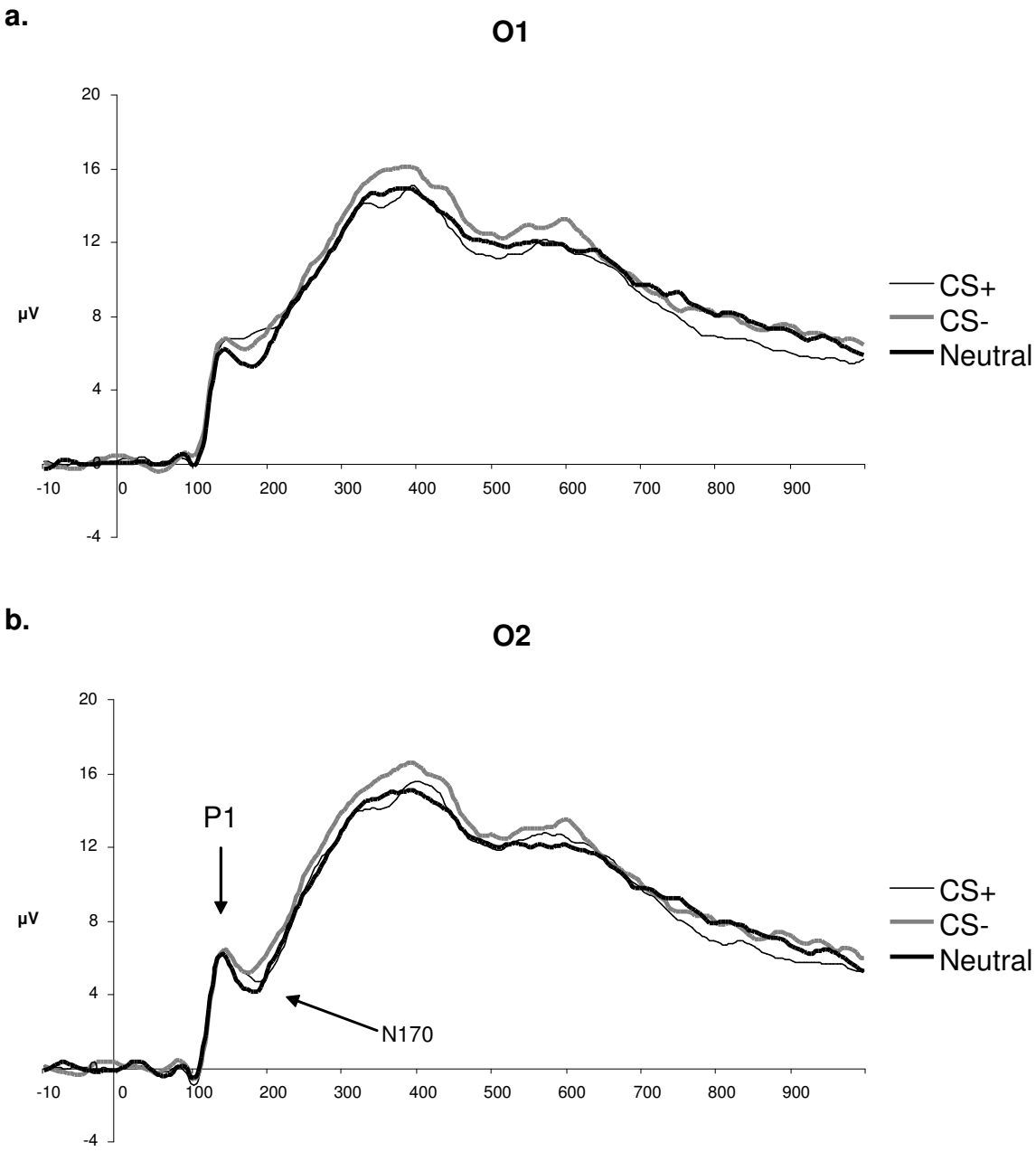


Figure 6.4. Grand averaged ERPs for three supraliminally presented face stimuli from the occipital sites O1 and O2.

6.3.2.3 Effects of trait/state anxiety and sex

Finally, we addressed the effects of state/ trait anxiety and sex in early ERP components by performing separate analyses for O1 and O2, adding STAI state scores and STAI trait scores as covariates and sex as between-subject factors in GLM RM (factors: stimulus type x experimental block).

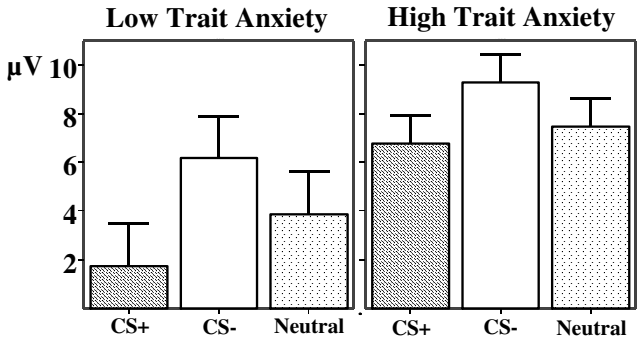


Figure 6.5. Mean P1 amplitudes (O2 electrode, subliminal presentation) and standard errors of the low-anxiety and high-anxiety subgroups. Post-hoc comparisons showed significant differences between all three conditions in the low-anxiety subgroup. In the high-anxiety subgroup, CS- was higher than CS+ and Neutral, but CS+ and Neutral did not differ significantly.

6.3.2.3.1 Subliminal presentation / Unconscious perception

P1 amplitudes: Analysis of the left occipital electrode (O1) revealed a significant effect of sex ($F(1,28) = 5.18$, $p < 0.05$): female subjects had higher P1 amplitudes than male subjects on all three stimulus types. State anxiety and trait anxiety did not have any significant effects.

Analysis of O2 yielded a main effect of trait anxiety ($F(1,28) = 5.94$, $p < 0.05$) and sex ($F(1,28) = 9.68$, $p < 0.005$): female subjects had higher P1 amplitudes than male subjects on all stimulus types. An stimulus type x trait anxiety interaction was also found ($F(2,56) = 3.63$, $p < 0.05$). To investigate the nature of the effect of trait anxiety and the stimulus type x trait anxiety interaction, we created two subgroups based on STAI trait scores relative to the median (Mdn = 34). One 'low trait anxiety' subgroup (n = 15, M = 27.2, SD = 3.1) having scores below the median and a 'high trait anxiety' subgroup (n = 17, M = 40.1, SD = 6.1) which had scores above the median. Post-hoc comparison of P1 amplitudes showed that subjects in the high trait anxiety subgroup had higher P1 amplitudes to all stimulus types as compared with subjects in the low trait anxiety subgroup. Furthermore, in the low trait anxiety subgroup amplitudes for CS- were higher than for Neutral stimuli ($p < 0.02$) and higher than CS+ ($p < 0.001$), while Neutral was higher than CS+ ($p< 0.05$). In the high anxiety subgroup however, mean CS- P1 amplitudes were higher than Neutral

stimuli ($p < 0.05$) and CS+ ($p < 0.01$), but the Neutral and CS+ conditions did not differ significantly (Figure 6.5).

N170 amplitudes: For the left occipital electrode (O1) a main effect of STAI State score was found ($F(1,28) = 5.55$, $p < 0.05$): subjects with lower STAI State scores had more negative N170 amplitudes than subjects with higher State scores. There were no significant effects of Trait anxiety or sex. For the right occipital electrode (O2) no significant effects were found.

P1 and N170 latencies: Analysis of the P1 and N170 latencies revealed no significant additional effects for any of the factors.

6.3.2.3.2 Supraliminal presentation / Conscious perception

P1 amplitudes: In the left occipital electrode (O1) a main effect of sex was found ($F(1,28) = 4.47$, $p < 0.05$): female subjects had higher P1 amplitudes compared to male subjects independent of the type of stimulus presented. Moreover, this analysis of the O1 electrode also showed a significant effect of stimulus type ($F(2,56) = 5.15$, $p < 0.01$). Tests of within subject-contrasts indicated that this effect was only significant for the conditioning contrast ($F(1,28) = 7.96$, $p < 0.01$). However, post-hoc comparisons revealed no significant differences between any two stimulus types.

Analysis of the right occipital electrode (O2) yielded significant effect for Trait and Sex: Female subjects had higher P1 amplitudes than male subjects ($F(1,28) = 8.25$, $p < 0.01$), while subjects with higher STAI Trait scored had higher P1 amplitudes than subjects with relatively low Trait scores ($F(1,28) = 5.62$, $p < 0.05$). No effects of stimulus type or other main factors were found.

N170 amplitudes: Analysis of the left occipital electrode (O1) showed a significant effect of State scores ($F(1,28) = 4.64$, $p < 0.05$): subjects with lower STAI State scores had more negative N170 amplitudes compared to subjects with higher State scores. No further effects were found. For the right occipital electrode (O2) no significant effects were found.

P1 and N170 latencies: Analysis of the P1 and N170 latencies revealed no significant additional effects for any of the factors.

6.3.2.4 Summary of results

Two early ERP components were found, both culminating on the occipitale electrodes O1 and O2. The first, positive component (P1) peaked between 130-150 ms after

onset of the masked stimulus. A second, negative component (N170) peaked between 190-200 ms after onset of the masked stimulus.

Interestingly, effects of stimulus type on P1 only occurred under conditions of subliminal presentation (unconscious perception). P1 amplitudes were sensitive to the effect of basic emotional expression as well as the effect of conditioning. P1 amplitudes were highest to CS- and lowest to CS+.

N170 amplitudes were only sensitive to the effect of conditioning when stimuli were presented subliminally (subconscious perception), while an effect of basic emotional expression on N170 only occurred under conditions of supraliminal presentation (conscious perception). Furthermore, increased latency for the conditioned angry face was found under supraliminal presentation.

P1 amplitudes were affected by gender of the subjects, as well as subjects' trait-score on the STAI with a specific interaction between trait-score and stimulus for the right occipital electrode under conditions of subliminal presentation. N170 amplitudes were not affected by gender or trait-score, but did show an effect of state-score, specifically for the left occipital electrode, both under supraliminal and subliminal presentation.

6.4 Discussion

6.4.1 General considerations

In the present study, we presented three types of emotional targets: Conditioned Angry faces (CS+), Unconditioned Angry faces (CS-) and Neutral faces (N) either subliminally or supraliminally. Since stimulus size, luminance and spatial location of the stimuli were controlled for in this experiment, we argue that the differences in P1 and N170 amplitude can only be attributed to the remaining stimulus characteristics, namely basic emotional expression of the face, leading to a difference between Neutral and CS-, and the effect of classical conditioning, evaluated though the difference between CS+ and CS-. The specific use of a backward masking design allowed separate analysis of the effects unconscious and conscious perception.

Considering the fact that two visual stimuli were presented in succession, with only a short inter stimulus interval, one might have expected to find two separate peaks in the ERPs: one related to the processing of the target and one related to the

mask. In our data, we did not find evidence for any 'double peak'. Nevertheless, considering the brief interval between the P1 and the N170, it could be argued that these two peaks reflect the successive processing of the target and the mask. In that case, the modulation of P1 amplitude would reflect processing of the different types of target that were presented, while the modulation of N170 amplitude would reflect processing of the different types of mask.

There are two arguments that substantiate this line of reasoning, the first being that the interval between the two peaks (approximately 50 ms) bears some relation with the inter stimulus interval between the onset of the target and the onset of the mask (i.e. 35 ms). Secondly, P1 amplitudes were only modulated when the (subliminally presented) targets were manipulated and not when the (supraliminally presented) masks were manipulated. It may therefore be inferred that the P1 is exclusively related to processing of the target and not to processing of the mask.

On the other hand however, manipulation of the targets did not result in a modulation of P1 alone, as N170 amplitudes were modulated under subliminal presentation as well. This implies that, even though the P1 was exclusively related to the target, N170 was at least partially related to the target as well and therefore not strictly related to the mask alone. Moreover, if P1 and N170 would reflect the same type of processing of the different stimuli but only at a different point in time, one would expect the modulation of N170 to the different types of mask to be comparable to the modulation of P1 to the different types of target. Our results show that this is clearly not the case: the P1 modulation under subliminal presentation was sensitive to the effects of both emotional expression and conditioning, whereas the modulation of the N170 to supraliminal presentation was only sensitive to emotional expression, specifically in the right hemisphere. Thirdly, P1 amplitudes were influenced by gender and trait anxiety of the subjects, while the N170 was only influenced by state anxiety.

We therefore argue that, in this study, the P1 is exclusively related to processing of the target, while the N170 is related to processing of both the target and the mask, thus reflecting a qualitatively different type of processing than reflected by P1.

6.4.2 P1

Several earlier studies have shown early ERP effects of various configural changes to face stimuli (Batty & Taylor, 2003; Halit et al., 2000; Itier & Taylor, 2002; Itier & Taylor, 2004; Linkenkaer-Hansen et al., 1998) and have suggested that the P1 may reflect global or holistic processing of face stimuli. Our study provides further evidence for the finding that changes in basic emotional expression have an effect on P1 amplitudes (Batty & Taylor, 2003) as we found higher P1 amplitudes for CS- than for neutral faces. However, our findings challenge the suggestion that the P1 only reflects global processing of facial configuration. If the emotion-dependent modulation of the P1 would only reflect global processing, one would expect P1 amplitudes for the CS+ and CS- not to be different, as these face stimuli share the same emotional expression. Since we found that P1 amplitudes for the CS+ were lower than the CS- in both O1 and O2 and even lower than Neutral faces in O2, this would constitute evidence for associative memory-related analysis of facial configuration within the same emotional expression. This analysis requires more detailed (i.e. local) and perhaps identity-related processing of facial configuration as within-category discrimination is needed to identify the one angry face (i.e. CS+) as being related to the white noise and the other angry face (i.e. CS-) as not being related to this aversive noise. Moreover, the difference between P1 amplitudes for CS- and CS+ stimuli does provide indirect evidence that the emotion-dependent modulation of P1 in our experiment reflects an early modulation of the visual cortex by the subcortical visual pathway and in particular the amygdala, as this structure has been shown to be very sensitive to the processing of aversively conditioned stimuli (Doron & LeDoux, 1999; LeDoux et al., 1984; Morris et al., 1998b).

The complete absence of the effects of basic emotional expression and conditioning under circumstances of conscious perception (i.e. supraliminal presentation) of the face stimuli implies that the modulation of P1 in our experiment is specifically related to unconscious processing of these stimuli. This provides further indirect evidence for the notion that the amygdala may play a crucial role in the modulation of P1, as this structure has been found to be particularly involved in processing subliminally presented facial expression (Morris et al., 1998b; Morris et al., 1999; Whalen et al., 1998).

At first sight, the conditioning dependent modulation of the P1 might appear to rule out thalamo-amygdalar processing as the responsible underlying mechanism,

because the coarseness of representations in the amygdala would probably not allow the level of precision that is required to differentiate between CS+ and CS-. While thalamo-amygdalar emotional processing may be very quick, it has been suggested that, due to the coarse representations in the amygdala, this speed may come at the price of a high false alarm rate (Büchel & Dolan, 2000), an inability to differentiate between stimuli with similar, yet distinct, characteristics (LeDoux, 1996) and an overgeneralization of responses (Zald, 2003).

One possible interpretation of the different P1 amplitudes to CS+ and CS- could be that, although these stimuli share the same facial expression, they might be processed as exponents of two different emotions. As the CS+ is associated with the startling experience of a loud white noise burst, it could be representing a fear-related stimulus, while the CS- would still be represent of anger. It has been suggested that in attended conditions, amygdala processing is limited to fearful stimuli, whereas under conditions of reduced stimulus analysis, as is the case in backward masking, the amygdala can extend its response to a broader range of potential threats (Anderson et al., 2003). In the light of this interpretation, presentation of the fear-related stimulus (CS+) resulted in decreased cortical activation compared to the anger-related stimulus (CS-), while the anger-related stimulus (CS-) resulted in increased cortical activation compared to the neutral stimuli. However, this interpretation does not explain why the 'fear-related' CS+ stimulus would have a lower P1 amplitude than Neutral stimuli while the 'anger-related' CS- stimulus would have a higher P1 amplitude compared to the Neutral stimuli.

Bearing in mind that classically conditioned stimuli may be processed adequately without cortical involvement (Doron & LeDoux, 1999; LeDoux et al., 1984; Morris et al., 1998b), we suggest that another explanation of the conditioning effect might be that the differences in P1 amplitude can be interpreted as a function of two factors, namely the emotional expression of the stimulus and the level of cortical processing that is required to generate an adequate response. Following this explanation, presentation of the CS- in our experiment enhanced cortical activity in both left and right occipital sites compared to the Neutral stimuli, as it was recognized as emotionally relevant (i.e. potentially threatening) but not previously associated with negative consequences such as the white noise, therefore requiring preferential access to attentive cortical processing. On the other hand, as the CS+ was recognized as emotionally relevant but also associated with the white noise and therefore not

requiring further attentive cortical processing, cortical activity for this stimulus was reduced.

6.4.3 N170

Analysis of N170 amplitudes showed a double dissociation between the effects of subliminal and supraliminal presentation: subliminal presentation of the stimuli only resulted in an effect of conditioning, while only an effect of basis emotional expression was found under circumstances of supraliminal presentation. This implies that the modulation of N170 amplitude under circumstances of subliminal presentation reflects a qualitatively different process than the N170 modulation found for supraliminal presentation of the stimuli.

Given that under conditions of unconscious processing all three stimuli shared a neutral mask, the reduced N170 amplitude to CS+ compared to CS- and neutral faces can only be attributed to differences between the masked stimuli. It is possible that the subliminally presented faces were processed sufficiently to produce the N170, even though conscious processing was prevented by the mask. Normal or even enhanced N170 amplitudes have previously been found in backward masking experiments (Liddell et al., 2004; Williams et al., 2004), while Vuilleumier and colleagues found normal N170 amplitudes after presentation of faces in the left visual field in a patient suffering from unilateral neglect and visual extinction for the left visual field (Vuilleumier et al., 2001). Assuming that the N170 modulation found under subliminal presentation was caused by the target stimulus itself (and not by the mask), our study provides further evidence that structural encoding of faces can take place outside the scope of awareness. However, this does not explain the double dissociation between the effects of subliminal and supraliminal presentation. Indeed, if normal structural encoding would have taken place despite the faces being masked, one would not expect any differences between N170 effects of subliminal versus supraliminal presentation.

It could also be possible that the N170 reflects structural encoding of the mask, but that this stage of processing is being influenced by re-entrant projections of the amygdala to this level of the visual stream, caused by properties of the target stimuli. In that case, it may come as no surprise that N170 amplitudes were specifically weaker to CS+ stimuli compared to CS- and neutral faces, since adequate processing of the CS+ does not require profound cortical processing.

Under circumstances of supraliminal presentation, N170 amplitudes to CS- were reduced compared to neutral faces. Since all targets had a similar, neutral, emotional expression, this effect can only be attributed to the properties of the mask. An emotional expression-induced modulation of the N170 has been previously reported by Batty and Taylor (2003), who found an increase in N170 amplitude to fearful faces compared to faces with neutral, happy, disgusted, surprised, sad or angry faces. In the same study, increased latencies for fearful, disgusted and sad faces were found compared to neutral, happy and surprised faces. Our study thus provides subsequent evidence that the N170 can be modulated dependent on the emotional expression of face stimuli. The increased latency for CS+ compared to neutral faces may reflect a processing disruption of face configuration due to including information arriving from the subcortical processing of the CS+ (Batty & Taylor, 2003).

6.4.4 Effects of gender, state anxiety and trait anxiety

We found that female subjects had higher P1 amplitudes than male subjects, independent of the type of stimulus that was presented. This effect of gender occurred under circumstances of both subliminal and supraliminal presentation but was limited to P1 amplitude alone, as no effect of gender was found on N170 amplitudes. Unfortunately, our design does not allow further substantiated evaluation of this issue.

An effect of self-reported state anxiety was found to be limited to N170 amplitudes in the left occipital electrode of both subliminal presentation and supraliminal presentation. Subjects with relatively high levels of state anxiety had weaker N170 amplitudes than those with relatively low anxiety at the time of the experiment. The levels of anxiety were reported immediately before the experiment (i.e. after instruction) and presumably did not change dramatically during the experiment. Sagiv and Bentin (2001) demonstrated that the N170 may reflect two kinds of processes: processing of holistic face configurations and face component analysis. The right hemisphere may have an advantage for configural processing, whereas the left hemisphere may be more involved in feature-based processing (De Gelder & Rouw, 2001). The weaker left hemisphere N170 amplitudes in subjects with high state anxiety might therefore be indicative for reduced feature-based processing of faces.

Testing the relation between facial processing and individual differences in experienced anxiety in everyday situations, we found that, under conditions of

subliminal presentation, people with relatively low trait-anxiety scores showed lower P1 amplitudes than people with a high level of trait anxiety. Furthermore, under conditions of subliminal presentation, subjects with a low trait anxiety score showed different P1 amplitudes to all three types of stimuli. On the other hand, subjects in the high-anxiety subgroup had higher P1 amplitudes to CS- stimuli compared to Neutral stimuli, but they exhibited no decrease in amplitude after presentation of the CS+. This result may very well indicate that subjects experiencing relatively more fear in everyday life may have higher cortical sensitivity to all facial stimuli, independent of emotional expression. Moreover, while subjects with low strait anxiety exhibited reduced cortical sensitivity to the CS+ compared to the Neutral stimuli, subjects in the high-anxiety group showed no decrease in cortical sensitivity after presentation of the CS+, even though this type of stimulus did not require cortical processing. This suggests that influences of subcortical structures (i.e. the amygdala) on cortical visual processing in people who experience high trait anxiety may be increased but also less specific than in subjects with relatively low trait anxiety. Subjects with high trait anxiety therefore, may be less successful at inhibiting attentive processing of fear-related stimuli.

Assuming that the P1 modulation indeed reflects projections of the amygdala to the visual cortex, our findings would be supplemental to fMRI studies that established increased amygdala activation in various psychiatric disorders (Birbaumer et al., 1998; Rauch et al., 2000; Sheline et al., 2001; Stein et al., 2002) and in people with high trait anxiety (Etkin et al., 2004). To our knowledge, this is the first ERP study linking cortical and subcortical emotional processing with the experience of anxiety in everyday situations in people with non-pathological fear.

6.5 Concluding remarks

In this study we found evidence that the P1 and N170 may reflect different neural mechanism of face processing. We suggest that the P1 is sensitive to unconscious processing of both global emotion-related aspects and more detailed identity-related aspects of faces. The modulation of P1 most likely reflects afferent projections from the amygdala to the early stages of visual processing, thus modulating early attentional processes. The intensity and specificity of these projections vary between

individuals and are related to trait anxiety. The modulation of N170 by subliminally presented conditioned faces may reflect later effects of the input from subcortical structures. When face stimuli are consciously processed, the N170 is only sensitive to basic emotional expression of the stimuli. Furthermore, P1 and N170 also reacted differentially to trait and state anxiety.

Applying this ERP paradigm in clinical populations, for instance comparing people with pathological fear or specific phobias with a normal population, might provide a better understanding of the persistence of some of these pathologies. For example, one might speculate that people with social phobia show a similar yet even more pronounced pattern of increased pre-attentive prioritization of emotional cues compared to the subjects with high trait anxiety in our study.

It would also be valuable to apply this ERP paradigm to neurological patients with impaired recognition of emotional expression in faces due to right-hemisphere stroke. As the complete or partial loss of emotional recognition in these patients is thought to be the result of degraded emotional facial representations in the cortex (Adolphs et al., 2000), one might expect to find unconscious emotional processing by subcortical structures as reflected by P1 amplitudes to be relatively intact.

For understanding the interplay of subcortical and cortical mechanisms underlying processing of facial emotions in humans, basic emotional expression is not the only factor to be taken into account. Our study suggests that emotional processing of face stimuli is the result of a crucial interaction between the level of awareness of the stimuli, the emotional expression of the face and the amount of cortical processing that is required to generate a behavioural response.

Our study has some methodological limitations. Firstly, activation of subcortical brain structures cannot be directly measured with ERPs to visual stimuli. We can therefore not be certain which structure is responsible for the emotion dependent pre-attentive modulation of visual processing. Secondly, as we only used a limited number of posterior leads, distributional information of the P1 and N170 in our experiment could not be calculated reliably. Future studies, ideally combining the high spatial resolution of fMRI with ERP measurements including neighbouring electrode sites T5 and T6, should allow more insight in the involvement of subcortical structures in the modulation of early ERP components to facial expressions and also permit more accurate calculation of scalp topographic maps.

Acknowledgements

We would like to thank Jorieke Wolterink and René Bax for their help collecting the data, and Phillipa Butcher and Reint Geuze for their critical and helpful comments.

References

Adolphs, R. (2002). Neural systems for recognizing emotion. *Current Opinion In Neurobiology, 12,* 169-177.

Adolphs, R., Damasio, H., Tranel, D., Cooper, G., & Damasio, A. R. (2000). A role for somatosensory cortices in the visual recognition of emotion as revealed by three-dimensional lesion mapping. *Journal of Neuroscience, 20,* 2683-2690.

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. R. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature, 372,* 669-672.

Amaral, D. G., Price, J. L., Pitkänen, A., & Carmichael, S. T. (1992). Anatomical organization of the primate amygdaloid complex. In J.P.Aggleton (Ed.), *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction* (pp. 1-66). New York: Wiley-Liss.

Anderson, A. K., Christoff, K., Panitz, D., De Rosa, E., & Gabrieli, J. D. E. (2003). Neural correlates of the automatic processing of threat facial signals. *Journal of Neuroscience, 23,* 5627-5633.

Armony, J. L. & Dolan, R. J. (2002). Modulation of spatial attention by fear-conditioned stimuli: an event-related fMRI study. *Neuropsychologia, 40,* 817-826.

Batty, M. & Taylor, M. J. (2003). Early processing of the six basic facial emotional expressions. *Cognitive Brain Research, 17,* 613-620.

Bentin, S., Allison, T., Puce, A., Perez, E., & McCarthy, G. (1996). Electrophysiological studies of face perception in humans. *Journal of Cognitive Neuroscience, 8,* 551-565.

Bentin, S. & Deouell, L. Y. (2000). Structural encoding and identification in face processing: ERP evidence for separate mechanisms. *Cognitive Neuropsychology, 17,* 35-54.

Birbaumer, N., Grodd, W., Diedrich, O., Klose, U., Erb, M., Lotze, M. et al. (1998). fMRI reveals amygdala activation to human faces in social phobics. *Neuroreport, 9,* 1223-1226.

Bruce, V. & Young, A. (1986). Understanding face recognition. *British Journal of Psychology, 77 (Pt 3),* 305-327.

Büchel, C. & Dolan, R. J. (2000). Classical fear conditioning in functional neuroimaging. *Current Opinion In Neurobiology, 10,* 219-223.

Davidson, R. J. & Irwin, W. (1999). The functional neuroanatomy of emotion and affective style. *Trends in Cognitive Sciences, 3,* 11-21.

De Gelder, B. & Rouw, R. (2001). Beyond localisation: a dynamical dual route account of face recognition. *Acta Psychologica, 107,* 183-207.

Di Lollo, V., Enns, J. T., & Rensink, R. A. (2000). Competition for consciousness among visual events: the psychophysics of reentrant visual processes. *Journal of Experimental Psychology: General, 129,* 481-507.

Doron, N. N. & LeDoux, J. E. (1999). Organization of projections to the lateral amygdala from auditory and visual areas of the thalamus in the rat. *Journal of Computational Neurology, 412,* 383-409.

Eger, E., Jedynak, A., Iwaki, T., & Skrandies, W. (2003). Rapid extraction of emotional expression: evidence from evoked potential fields during brief presentation of face stimuli. *Neuropsychologia, 41,* 808-817.

Eimer, M. (1998). Does the face-specific N170 component reflect the activity of a specialized eye processor? *Neuroreport, 9,* 2945-2948.

Eimer, M. (2000a). Effects of face inversion on the structural encoding and recognition of faces. Evidence from event-related brain potentials. *Cognitive Brain Research, 10,* 145-158.

Eimer, M. (2000b). The face-specific N170 component reflects late stages in the structural encoding of faces. *Neuroreport, 11,* 2319-2324.

Eimer, M. & Holmes, A. (2002). An ERP study on the time course of emotional face processing. *Neuroreport, 13,* 427-431.

Eimer, M. & McCarthy, R. A. (1999). Prosopagnosia and structural encoding of faces: evidence from event-related potentials. *Neuroreport, 10,* 255-259.

Ekman, P. & Friesen, W. V. (1976). *Pictures of Facial Affect*. Palo Alto: Consulting Psychologists Press.

Enns, J. T. & Di Lollo, V. (2000). What's new in visual masking? *Trends in Cognitive Sciences, 4,* 345-352.

Etkin, A., Klemenhagen, K. C., Dudman, J. T., Rogan, M. T., Hen, R., Kandel, E. R. et al. (2004). Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. *Neuron, 44,* 1043-1055.

Foxe, J. J. & Simpson, G. V. (2002). Flow of activation from V1 to frontal cortex in humans. A framework for defining "early" visual processing. *Experimental Brain Research, 142,* 139-150.

Gratton, G., Coles, M. G. H., & Donchin, E. (1983). A new method for off-line removal of ocular artefact. *Electroencephalography and Clinical Neurophysiology, 55,* 468-484.

Halit, H., De Haan, M., & Johnson, M. H. (2000). Modulation of event-related potentials by prototypical and atypical faces. *Neuroreport, 11,* 1871-1875.

Hariri, A. R., Bookheimer, S. Y., & Mazziotta, J. C. (2000). Modulating emotional responses: effects of a neocortical network on the limbic system. *Neuroreport, 11,* 43-48.

Heinze, H. J., Mangun, G. R., Burchert, W., Hinrichs, H., Scholz, M., Munte, T. F. et al. (1994). Combined spatial and temporal imaging of brain activity during visual selective attention in humans. *Nature, 372,* 543-546.

Hermans, D. (1994). De Zelf-Beoordelings-Vragenlijst (ZBV) [The State-Trait Anxiety Inventory (STAI)]. *Gedragstherapie, 27,* 145-148.

Holmes, A., Vuilleumier, P., & Eimer, M. (2003). The processing of emotional facial expression is gated by spatial attention: evidence from event-related brain potentials. *Cognitive Brain Research, 16,* 174-184.

Hopf, J. M. & Mangun, G. R. (2000). Shifting visual attention in space: an electrophysiological analysis using high spatial resolution mapping. *Clinical Neurophysiology, 111,* 1241-1257.

Itier, R. J. & Taylor, M. J. (2002). Inversion and contrast polarity reversal affect both encoding and recognition processes of unfamiliar faces: a repetition study using ERPs. *Neuroimage., 15,* 353-372.

Itier, R. J. & Taylor, M. J. (2004). Effects of repetition learning on upright, inverted and contrast-reversed face processing using ERPs. *Neuroimage., 21,* 1518-1532.

LeDoux, J. E. (1996). *The Emotional Brain*. New York: Touchstone.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience, 23,* 155-184.

LeDoux, J. E., Sakaguchi, A., & Reis, D. J. (1984). Subcortical efferent projections of the medial geniculate nucleus mediate emotional responses conditioned to acoustic stimuli. *Journal of Neuroscience, 4,* 683-698.

Liddell, B. J., Williams, L. M., Rathjen, J., Shevrin, H., & Gordon, E. (2004). A temporal dissociation of subliminal versus supraliminal fear perception: an event-related potential study. *Journal of Cognitive Neuroscience, 16,* 479-486.

Linkenkaer-Hansen, K., Palva, J. M., Sams, M., Hietanen, J. K., Aronen, H. J., & Ilmoniemi, R. J. (1998). Face-selective processing in human extrastriate cortex around 120 ms after stimulus onset revealed by magneto- and electroencephalography. *Neuroscience Letters, 253,* 147-150.

Liu, J., Harris, A., & Kanwisher, N. (2002). Stages of processing in face perception: an MEG study. *Nature Neuroscience, 5,* 910-916.

Martinez, A., Di Russo, F., Anllo-Vento, L., & Hillyard, S. A. (2001). Electrophysiological analysis of cortical mechanisms of selective attention to high and low spatial frequencies. *Clinical Neurophysiology, 112,* 1980-1998.

Mazurski, E. J., Bond, N. W., Siddle, D. A. T., & Lovibond, P. F. (1996). Conditioning with facial expressions of emotion: effects of CS sex and age. *Psychophysiology, 33,* 416-425.

Morris, J. S., DeGelder, B., Weiskrantz, L., & Dolan, R. J. (2001). Differential extrageniculostriate and amygdala responses to presentation of emotional faces in a cortically blind field. *Brain, 124,* 1241-1252.

Morris, J. S., Friston, K. J., Buchel, C., Frith, C., Young, A. W., Calder, A. J. et al. (1998a). A neuromodulatory role for the human amygdala in processing emotional facial expressions. *Brain, 121,* 47-57.

Morris, J. S., Frith, C. D., Perrett, D. I., Rowland, D., Young, A. W., Calder, A. J. et al. (1996). A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature, 383,* 812-815.

Morris, J. S., Öhman, A., & Dolan, R. J. (1998b). Conscious and unconscious emotional learning in the human amygdala. *Nature, 393,* 467-470.

Morris, J. S., Öhman, A., & Dolan, R. J. (1999). A subcortical pathway to the right amygdala mediating "unseen" fear. *Proceedings of the National Academy of Sciences of the United Stated of America, 96,* 1680-1685.

Pizzagalli, D., Regard, M., & Lehmann, D. (1999). Rapid emotional face processing in the human right and left brain hemispheres: an ERP study. *Neuroreport, 10,* 2691-2698.

Rauch, S. L., Whalen, P. J., Shin, L. M., McInerney, S. C., Macklin, M. L., Lasko, N. B. et al. (2000). Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biological Psychiatry, 47,* 769-776.

Sagiv, N. & Bentin, S. (2001). Structural encoding of human and schematic faces: holistic and part-based processes. *Journal of Cognitive Neuroscience, 13,* 937-951.

Sheline, Y. I., Barcg, D. M., Donnely, J. M., Ollinger, J. M., Snyder, A. Z., & Mintun, M. A. (2001). Increased amygdala response to masked emotional faces in depressed subjects resolves with intidepressant treatment: an fMRI study. *Biological Psychiatry, 50,* 651-658.

Spielberger, C. D., Gorsuch, R. L., & Lushene, R. E. (1970). *STAI Manual for the State-Trait Anxiety Inventory*. Palo Alto: Consulting Psychologists Press.

Stein, M. B., Goldin, P. R., Sareen, J., Zorrilla, L. T. E., & Brown, G. G. (2002). Increased amygdala activation to angry and contemptuous faces in generalized social phobia. *Archives of General Psychiatry, 59,* 1027-1034.

Streit, M., Ioannides, A. A., Liu, L., Wolwer, W., Dammers, J., Gross, J. et al. (1999). Neurophysiological correlates of the recognition of facial expressions of emotion as revealed by magnetoencephalography. *Cognitive Brain Research, 7,* 481-491.

Vuilleumier, P., Armony, J. L., Clarke, K., Husain, M., Driver, J., & Dolan, R. J. (2002). Neural response to emotional faces with and without awareness: event-related fMRI in a parietal patient with visual extinction and spatial neglect. *Neuropsychologia, 40,* 2156-2166.

Vuilleumier, P., Sagiv, N., Hazeltine, E., Poldrack, R. A., Swick, D., Rafal, R. D. et al. (2001). Neural fate of seen and unseen faces in visuospatial neglect: a combined event-related functional MRI and event-related potential study. *Proceedings of the National Academy of Sciences of the United Stated of America, 98,* 3495-3500.

Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., & Jenike, M. A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *Journal of Neuroscience, 18,* 411-418.

Williams, L. M., Liddell, B. J., Rathjen, J., Brown, K. J., Gray, J., Phillips, M. et al. (2004). Mapping the time course of nonconscious and conscious perception of fear: an integration of central and peripheral measures. *Human Brain Mapping, 21,* 64-74.

Zald, D. H. (2003). The human amygdala and the emotional evaluation of sensory stimuli. *Brain Research Reviews, 41,* 88-123.

Chapter 7

Conscious and unconscious processing of fear after right amygdala damage: a single case ERP study

Joost Heutink, Wiebo H. Brouwer, Bauke M. de Jong & Anke Bouma

Abstract

In this study, we describe a 58-year old male patient (FZ) who has a right-amygdala lesion as a result of a temporal lobe infarction. FZ is unable to recognize fearful facial expressions. Instead, he always misinterprets fearful expressions for surprise. Employing EEG/ERP measures, we investigated whether presentation of fearful and surprised facial expressions would lead to different response patterns. We measured ERPs to aversively conditioned and unconditioned fearful faces.

We compared ERPs elicited by supraliminally and subliminally presented conditioned fearful faces (CS+), unconditioned fearful faces (CS-) and surprised faces. Supraliminal presentation of CS- and surprised faces lead to differences in P170 and Late Negativity (LN) ERP components. This indicates that, despite FZ's inability to explicitly recognize fearful expressions, implicit recognition of fear is still intact. Differences between ERPs to CS+ and CS- were only found when these stimuli were presented subliminally. This indicates that intact right amygdala function is not necessary for aversive conditioning.

Previous studies have stressed the importance of the right amygdala for discriminating facial emotional expressions and for classical conditioning. Our study suggests that the right amygdala is necessary for explicit recognition of fear, while implicit recognition of fear and classical conditioning may still occur without the right amygdala.

7.1 Introduction

The human amygdala, which is located in the anterior medial part of the temporal lobes, plays an important role in emotional processing. It is involved in the evaluation of and response to emotional stimuli (LeDoux, 2000; Zald, 2003), as well as the consolidation of emotional information (LeDoux, 1993). Apart from receiving more elaborate input from cortical areas such as the temporal lobes (Amaral et al., 1992) or the prefrontal cortex (Davidson & Irwin, 1999; Keightley et al., 2003), the amygdala receives crude sensory information directly from the thalamic sensory relay nuclei (Doron & LeDoux, 1999; Mazurski et al., 1996). This allows immediate responses to biologically and socially relevant stimuli, such as facial emotional expressions (Adolphs et al., 1994; Adolphs et al., 1998) and aversively conditioned stimuli (Doron & LeDoux, 1999; LeDoux et al., 1984; Morris et al., 1998), even outside the scope of human consciousness (Whalen et al., 1998).

From the literature, a rather consistent picture arises with regard to the consequences of bilateral amygdala damage. Most frequently impaired recognition of fearful expressions in faces is reported (Adolphs et al., 1994; Adolphs et al., 1999; Schmolck & Squire, 2001; Wang et al., 2003), although processing of other negative facial expressions such as sadness and anger may be impaired as well (Adolphs et al., 1999; Adolphs & Tranel, 2004; Schmolck & Squire, 2001; Scott et al., 1997). It is less clear from the literature what the consequences of unilateral amygdala damage are. Reports suggest that unilateral amygdala patients may be impaired at a range of tasks, such as simple and complex conditioning tasks (LaBar et al., 1995) and recognition of complex emotional expressions in faces (Adolphs et al., 2002) and emotional scenes (Adolphs & Tranel, 2003). Recognition of basic emotional expressions or judging a person's trustworthiness or approachability may be unimpaired (Adolphs et al., 1998) in these patients.

Studies comparing patients with left unilateral amygdala lesions with right-amygdala patients indicate that right amygdala patients may have diminished fear potentiated startle when viewing emotional pictures (Funayama et al., 2001), may be more impaired at rating complex emotional scenes (Adolphs & Tranel, 2003), and may be more impaired at recognizing basic emotional expressions (Anderson et al., 2000) as compared to patients with left-amygdala damage. Left-amygdala patients on the other hand, may have diminished fear potentiated startle when they receive verbal

instructions that a certain type of stimulus predicts receiving a shock (Funayama et al., 2001), or may be impaired at tasks involving verbal memory for emotional stimuli (Buchanan et al., 2001; Frank & Tomaz, 2003).

In this study, we describe a 58-year old male patient (FZ) who has a right-amygdala lesion as a result of temporal lobe infarction. His lesion stretches from the right-hemisphere temporal pole to the fusiform areas, covering the lower 2/3 of the temporal lobe. FZ is almost completely unable to recognize the facial expression of fear. Instead, on neuropsychological tests of emotion recognition, he always misinterprets fearful expressions for surprise. This type of consistent misinterpretation of a specific emotion has been previously observed in a group of bilateral amygdala patients (Adolphs et al., 1999) but, to the best of our knowledge, not in patients with unilateral lesions. FZ therefore provides a useful addition to earlier described cases of unilateral amygdala damage. Neuropsychological assessment revealed that FZ has a specific impairment in recognizing fear, which cannot be attributed to FZ's general perceptual deficits such as his homonymous visual field defect of the upper left quadrant or his mild impairment for the perception of faces.

Although FZ is unable to tell the difference between a fearful facial expression and a surprised expression, this does not necessarily imply that fearful and surprised expressions are processed in exactly the same way in his brain. For instance, in patients with prosopagnosia, the inability to recognize previously familiar faces (Damasio, 1985), implicit ('covert') recognition may be still intact, in the absence of explicit ('overt') recognition (Bauer, 1984; De Haan et al., 1987; De Haan et al., 1991; Renault et al., 1989; Tranel et al., 1995; Tranel & Damasio, 1988). We therefore employed EEG/ERP measures to investigate whether processing of fearful facial expressions would lead to a different neuronal response pattern compared to processing of surprised facial expressions. Such a difference would indicate a difference between covert and overt emotional processing in FZ.

It has been suggested that the left amygdala is primarily involved in conscious perception of fear, thus producing verbal labelling of emotions by left-hemisphere dominated language networks, whereas the right amygdala is primarily involved in the unconscious processing of fear (Funayama et al., 2001; Morris et al., 1998). Employing PET in normal subjects, Morris et al. (1998) presented two angry faces and two neutral faces. One of the angry faces (the CS+) was previously paired with a white noise burst, while the other angry face (the CS-) was not paired with this white

noise. Subjects were shown masked presentations of one of the four faces. Each trial consisted of a brief presentation of a face, followed by a brief presentation of another face (the mask). The presentation of the mask prevented conscious processing of the first face. Morris et al. found that the right amygdala was activated during presentation of trials in which the CS+ was masked by a neutral face, while the left amygdala did not show any activation during these trials. The left amygdala, however, was activated in trials in which a neutral face was masked by the CS+, while right amygdala activation was absent during these trials.

Using an adaptation for EEG/ERP measurements of the method of Morris et al. (Morris et al., 1998), we investigated conscious versus unconscious processing of aversively conditioned fearful faces (CS+), unconditioned fearful faces (CS-) and Surprised faces (S) in FZ. Since only FZ's left amygdala is intact, we hypothesized that, under circumstances of conscious perception, processing of aversely conditioned stimuli would differ from unconditioned stimuli as measured by EEG/ERP. Under circumstances of unconscious (i.e. masked) perception however, we would expect processing of aversely conditioned and unconditioned stimuli not to be different.

7.2 Case History

7.2.1 Medical history

FZ is a 58-year old, right-handed man with 16 years of formal education. At the age of 47, he suffered from temporary right-hand clumsiness and dysarthria, which was attributed to a small ischaemic left-hemisphere lesion just above the nucleus caudatus (corona radiata). When FZ was 56, he was inflicted by a haemorrhage along the external rim of the right basal ganglia. Due to the mass effect of this haematoma, the temporal branch of the middle cerebral artery was compromised, leading to an additional right temporal lobe infarction. General clinical neurological examination at a later stage after the second incident revealed only minor deficit, consisting of hypaesthesia on the left side of the body and deficit in the left upper quadrant of the visual field. Tendon stretch reflexes were slightly more brisk on the left side. Structural MRI (3 years after the cerebral haemorrhage) showed a lesion in the lower 2/3 of the right temporal lobe, extending from the temporal pole (including the amygdala) to the fusiform area (see Figure 7.1). Resorption of the 2001 haematoma

left a small lesion in the capsula externa, just outside the putamen. FZ had been a successful self-employed engineer in robot technology until the age of 55. He was referred to the neuropsychology unit of the University Medical Centre in Groningen (UMCG) to evaluate cognitive functioning and fitness to drive two years after his right-hemisphere lesion.

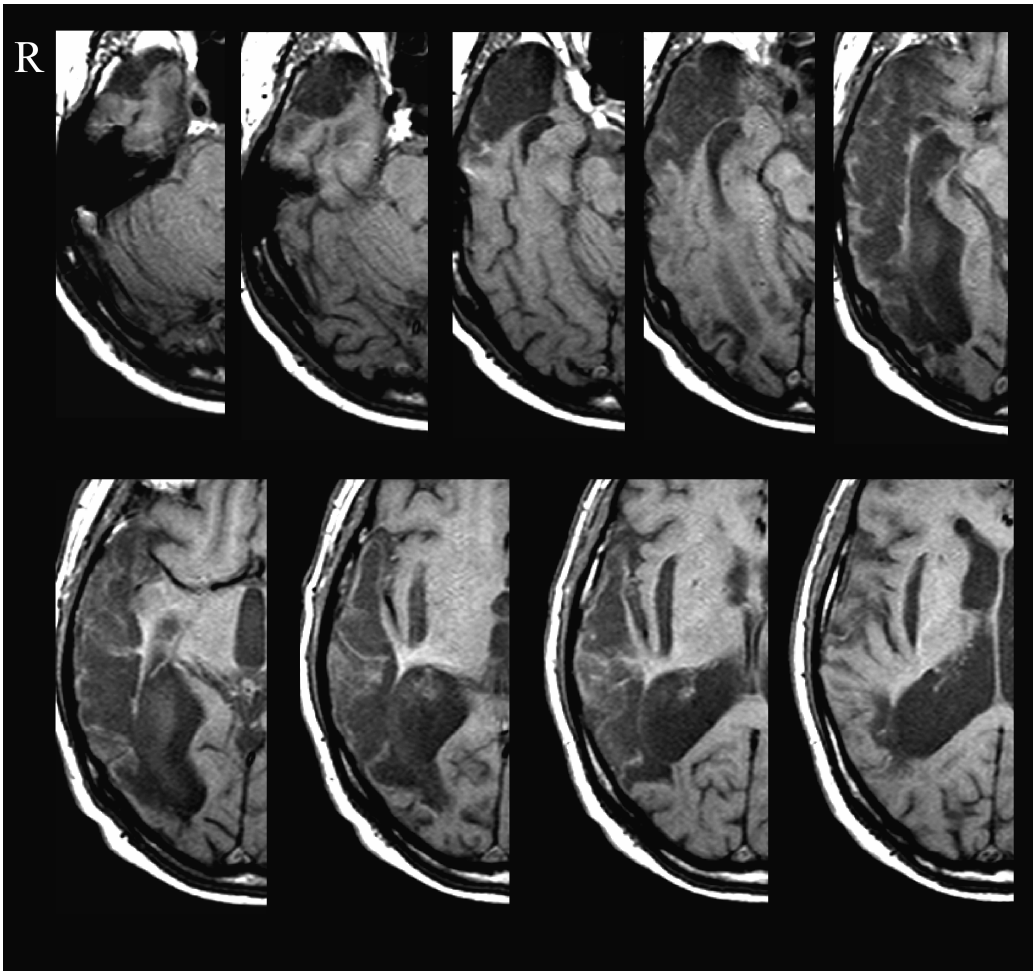


Figure 7.1. T1 MRI of FZ (at age 58) showing his right temporal brain lesion. Left side of the image = Right side of the brain.

7.2.2 Assessment of visual field, neglect and visual extinction

The subtest Visual Field of the Test for Attention and Performance (TAP) (Zimmerman & Fimm, 1996) indicated a field loss for the left visual field. Goldmann perimetry showed a clear visual field defect of the upper left quadrant, with macular sparing. This field defect can be directly related to the lesion in the right temporal lobe. FZ omitted seven items on Bells test (Gauthier et al., 1989), of which five on the far left and two on the right side of the paper. On a questionnaire for detecting everyday problems in patients with unilateral neglect (Towle & Lincoln, 1991), FZ indicated no complaints related to unilateral neglect. FZ performed accurately on a copying task and showed no visual extinction. Thus, FZ had a field deficit for the upper left quadrant with a poor searching strategy, but no clear signs of unilateral neglect.

7.2.3 Intelligence and Memory

On a shortened version of the Groningen Intelligence Test (Luteijn & Van der Ploeg, 1983), FZ's estimated IQ was above average (115-121), which is conform his level of education.

On a test for verbal memory (15 Word-Test: Saan & Deelman, 1986), FZ's score was above-average to high compared to males of similar age and education (acquisition: 10^{th} decile; delayed recall 7-8^{th} decile). On the subtest Recognition Memory Test for Faces of the Recognition Memory test (Warrington, 1984; Dutch adaptation and norms: Diesfeldt & Vink, 1989; Van de Berg et al., 1995), FZ only correctly recognized 31 of 50 faces (< 5^{th} percentile).

7.2.4 Visual perception and perception of faces

Performance on the Judgement of Line Orientation Test (Benton et al., 1983a) was high-average (26 out of 30 correct; 8^{th} decile). On the short form of Benton' Facial Recognition Test (Benton et al., 1983b), FZ had a corrected score of 39, indicating borderline impairment for the perception of faces. We showed FZ a number photographs of still life paintings by various Dutch 16^{th} century master painters. These pictures were intermingled with paintings of the Italian renaissance artist Giuseppe Arcimboldo (1527-1593), who painted still lifes of groupings of vegetables, fruits, flowers and animals in such a way that they can be perceived as a human face.

FZ could name all details, such as varieties of flowers and fruits in all paintings, but was unable to recognize the faces in the paintings by Arcimboldo.

There were some indications of an integrative agnosia, especially holistic perception. However, there were no indications for an associative prosopagnosia since FZ recognized and named 21 out of 24 photographs of national and international celebrities (no norms available). Furthermore, FZ did not miss any items on an Overlapping Figures test.

7.2.5 Speed of information processing and attention

Speed of information processing was assessed using a reaction time apparatus that divides each reaction time into a decision time (DT) and a motor time (MT) (Van Zomeren & Deelman, 1978). The visual reaction time test (VRT) consists of 3 subtests: a simple reaction time test with one stimulus, a tests with four stimuli and a dual task with four visual stimuli and an auditory stimulus. On all three subtests of the VRT, FZ's DTs were very slow (1st decile), while MTs were very fast (8th decile).

Selective attention was assessed with the Dutch version of the Stroop colour-word test (Schmand et al., 2003). Performance on the Word card I was below average (3rd decile); Colour card II high-average (7th -8th decile); Colour-Word card III was high-average (7th -8th decile).

On the Trail Making Test (TMT) (Reitan, 1955; Dutch norms: Schmand & De Koning, 2003), FZ needed 105 s to complete Form A (1st percentile) and 228 s to complete Form B (1st percentile).

FZ may thus have slow speed of information processing, however, reaction times may still be normal due to his fast motor reactions. There are no indications for a deficit in selective attention as performance on the Stroop test was normal. Although FZ's performance on the TMT is impaired, it is unclear to which extend his performance may be influenced by the aforementioned visual field deficit and his poor search strategy.

7.2.6 Emotional recognition

Recognition of facial emotional expression was assessed with the Ekman 60 Faces test and the Emotion Hexagon test of the FEEST (Young et al., 2002). The Ekman 60 Faces test uses 60 photos from a Ekman and Friesen's series of pictures of facial affect (Ekman & Friesen, 1976) to assess recognition of six basic emotions (anger,

disgust, fear, happiness, sadness and surprise). FZ's overall score was 45, which is just above cut-off for the group aged 41-60 (Mean 51.2, Cut-off 43). Recognition of fear, however, was below cut-off. FZ only recognized 2 out of 10 correctly (Mean 7, Cut-off 4). On all incorrect responses, FZ misinterpreted the emotion fear as surprise.

The Emotion Hexagon test consists of 120 stimuli of graded difficulty. Faces from the Ekman and Friesen series are morphed using computer technique to create more ambiguous facial expressions than those used in the Ekman 60 Faces test. FZ's total score was 82, which is below cut-off for the group aged 41-60 (Mean 108.1, Cut-off 92). FZ had normal recognition of all emotions except anger and fear. He recognized 9 out of 20 faces with an angry expression (Mean 17.6, Cut-off 13) and only 2 out of 20 faces with a fearful expression (Mean 16.2, Cut-off 10). Out of the 18 incorrect responses on fearful faces, FZ misinterpreted 17 fearful faces for surprise; on one incorrect response he mistook it for happiness.

7.2.7 Summary neuropsychological assessment

FZ is a 58-year old man with a large lesion of his right temporal lobe, including the amygdala, and two minor lesions in both the left and right hemisphere. As a result of his lesion in the temporal lobe, he has a visual field defect with macular sparing but no unilateral neglect. His intelligence is above average to high, and his verbal memory is very good. FZ has no associative prosopagnosia but does have a borderline impairment for perception of faces, probably due to impaired holistic perception. FZ has normal perception of most emotional facial expressions, except for fear and – to a much lesser extent - anger. On almost all occasions, FZ misinterprets fearful facial expressions for surprised expressions. This impairment for recognizing fear is most likely related to his right amygdala damage.

7.3 Method

7.3.1 Experimental paradigm

In this experiment we employed an ERP paradigm to compare conscious and unconscious processing of fearful and surprised facial expressions. To this end, pictures of fearful and surprised facial expressions were presented either as a stimulus or as a mask in a backward masking paradigm. Two fearful faces were used in this

experiment. One fearful face served as aversively conditioned stimulus (CS+) and was paired to a white noise burst on a number of conditioning blocks preceding each EEG recording session. The other fearful face was never paired with the white noise burst and served as the unconditioned stimulus (CS-). In the unconscious processing condition, we compared ERPs to subliminally presented pictures of the CS+, CS- or Surprised faces. Each of these brief presentations was followed by a mask which consisted of a surprised face. In the conscious processing condition we subliminally presented pictures of surprised faces followed by a mask that consisted of either the CS+, CS- or a Surprised face.

7.3.2 Stimuli

The stimuli consisted of eleven digital greyscale photographs of different faces from Ekman and Friesen's standard set of faces (Ekman & Friesen, 1976). Nine faces had a surprised expression and two faces had a fearful expression. The two faces with a fearful expression were selected after the following procedure. On ten separate occasions, FZ was presented a subset of the Ekman and Friesen consisting of 24 images, four of each basic emotional expression (anger, disgust, fear, happiness, sadness and surprise). The two faces with a fearful facial expression that were selected for the experiment had never been correctly recognized by FZ during neuropsychological assessment.

All pictures were modified is such a way that distracting features in the outer contours, such as neck and hair were made black and that all stimuli had similar size and luminance. All stimuli were presented in the centre of a 17 inch monitor (resolution 800 x 600, refresh rate 16.7 ms) at 70 cm viewing distance (6,5° visual angle).

7.3.3 Procedure

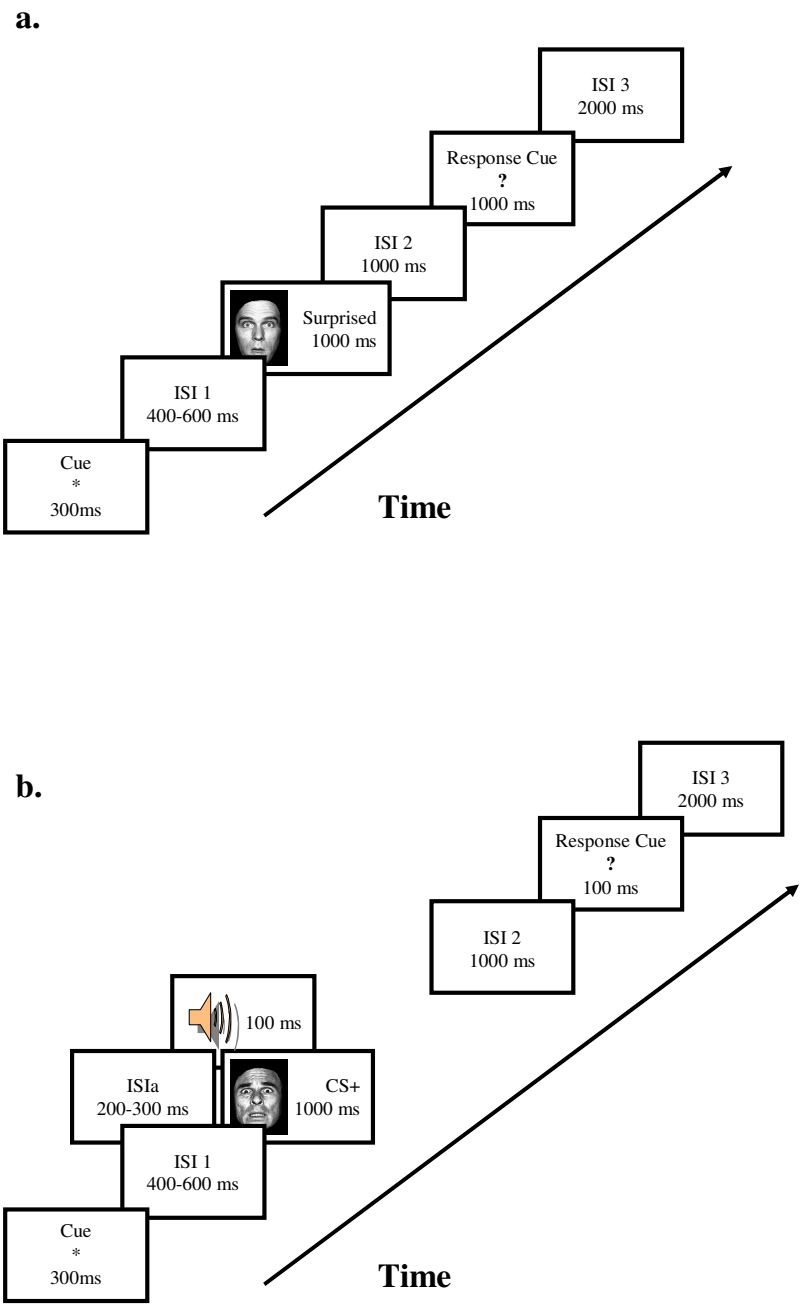
Conditioning procedure: In 22 conditioning blocks, each preceding an experimental block during which the ERP recordings took place, FZ was presented a sequence of 50 trials. Each trial consisted of the following sequence (Figure 7.2a): a warning cue '*' (300 ms) in the centre of the screen, followed by a black screen (400-600 ms), a greyscale image of a face (1000 ms), a black screen (1000 ms), and a response cue '?' (1000 ms), followed by another black screen (2000 ms). Half of the facial stimuli consisted of the nine surprised faces (S), the other half consisted of one of the fearful

faces. Fifty percent (i.e. alternately 12 or 13 out of 25) of the presentations of the fearful face (CS+) were accompanied by a 90 dB white noise burst of 100 ms (Figure 7.2b).

Experimental task: In the 22 experimental blocks, which each followed a conditioning block, the unconditioned fearful face (CS-) was added to the set of presented stimuli. In each experimental block, FZ viewed a sequence of 60 trials, but now each trial consisted of a pair of faces, namely a subliminally presented target followed by a supraliminally presented mask. In the experimental blocks, the CS+ was never paired with the white noise burst. Each trial consisted of the following sequence (Figure 7.2c): a warning cue '*' (300 ms) in the centre of the screen, followed by a black screen (400-600 ms), the target (16.7 ms), a black screen (16.7 ms), the mask (1000 ms), a black screen (1000 ms), and a response cue '?' (1000 ms), followed by another black screen (1960 ms). The 16.7 ms black screen between the presentation of the target and the mask was added to prevent the possibility that the target-mask sequence might be perceived as the presentation of a single face with a quickly changing expression. This backward masking sequence was piloted in 6 normal subjects prior to the experiment to ensure that the target could not be recognized. FZ reported that he had never been aware of a brief 'flash' before the face was presented, let alone recognize the masked stimulus.

In each experimental block, five different stimulus conditions were presented in pseudo-random order (Table 7.1): (*1*) subliminal CS+, in which the CS+ fearful face (previously paired with white noise) was the target and a surprised face was the mask; (*2*) subliminal CS-, in which the CS- fearful face (not paired with white noise) was the target and a surprised face was the mask; (*3*) supraliminal CS+, in which a surprised face was the masked target and the CS+ the mask; (*4*) supraliminal CS-, in which a surprised face was the masked target and the CS- the mask; (*5*) supraliminal surprised face, in which both the subliminal target and the supraliminal mask consisted of a surprised face. Each of the five conditions was presented 12 times in every experimental block. The five different stimulus conditions were presented randomly in each experimental block, with the following restrictions: the same stimulus condition was never presented two times in succession and the same face was not presented twice in a single target-mask combination.

FZ was tested on four occasions. During the first session, four experimental blocks were completed, and six blocks in each following session. The total amount of experimental blocks was 22. In total, each stimulus condition was repeated 264 times.



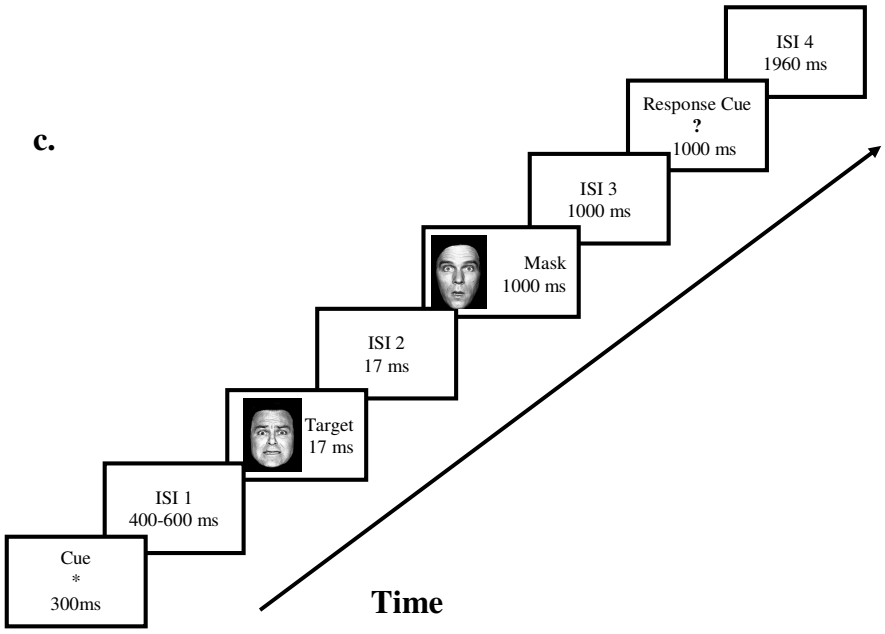


Figure 7.2. Schematic outline of a single trial of the conditioning blocks (**a.** and **b.**) and the experimental blocks (**c.**). **(a)** presentation of a trial with a surprised face; (**b.**) presentation of a trial with a fearful face, which was coupled with a 90dB white noise burst in 50% of presentations; (**c.**) single trial of a subliminally presented target and a supraliminally presented mask. During the experimental blocks, CS+ was never paired with the white noise burst.

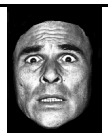
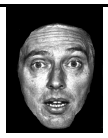
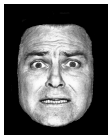
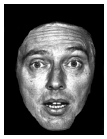
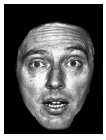
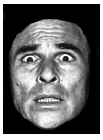
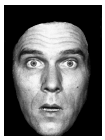
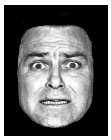
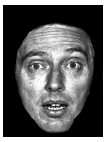
Sham task: To ensure that FZ would be looking carefully at each face that was presented during the experiment, a sham task was designed. In both the conditioning blocks and the experimental blocks, FZ was asked to press a foot-pedal if the presented face met certain criteria, which changed every new conditioning block. FZ was told that the conditioning blocks were merely a practice for the 'real' experimental blocks, during which EEG recording took place. He was also told not to be distracted by the noises that were administered via the headphone during the 'practicing blocks'. The sham task did not require emotional evaluation of the faces and none of the given instructions were related to the differences in emotional expression between the faces. The consecutive instructions for the sham task were: "press the foot pedal with your right foot if you think the picture is of a woman older than 50 years" (conditioning block 1 and experimental block 1); "press your left foot for a man older than 55" (blocks 2); "press your right foot for a woman younger than

25" (blocks 3); "press you left foot for a woman older than 50" (blocks 4); "press your right foot for a man older than 55" (blocks 5); "press your left foot for a woman younger than 25" (blocks 6). These instructions were chosen in such a way that a maximum of 6 responses were required in each block. Unspeeded responses were given by FZ when the response cue ('?') appeared on the screen.

7.3.4 Electrophysiological recordings

Experiments were conducted in a Faraday chamber. EEG data were recorded from 16 electrodes corresponding to the traditional 10/20 system: Fp1, Fp2, F3, Fz, F4, C3, Cz, C4, P3, Pz, P4, T3, T4, O1, Oz and O2 with the left and right mastoid as references. A standard electrodecap (ElectroCap) with Tn (tin) electrodes was used to apply the electrodes. Combined horizontal and vertical EOG was measured by Ag/AgCl electrodes placed above the left eye and on the outer canthus of the right eye.

Table 7.1. Five types of conditions presented in the experimental task. Each subliminally presented Target stimulus was followed by a supraliminally presented Mask.

Condition	Target (17 ms)		Mask (1000 ms)	
1.	CS+		Surprised	
2.	CS-		Surprised	
3.	Surprised		CS+	
4.	Surprised		CS-	
5.	Surprised		Surprised	

Impedance was kept below 5 kΩ. EOG and EEG were amplified with a 10 s time constant and a 200 Hz low pass filter, sampled at 1000 Hz, digitally filtered with a 30 Hz lowpass Hamming filter and on-line reduced to a sample frequency of 200 Hz.ERPs were averaged off-line using BrainVision© software, automatically rejecting trials with EEG artefacts (i.e. activity above 195 μV or below -195μV). Contribution of eye movements and blinks was corrected (Gratton et al., 1983). A baseline voltage of 200 ms preceding stimulus onset was taken. For all ERPs, the start of the presentation of the subliminally presented target was time zero for averaging.

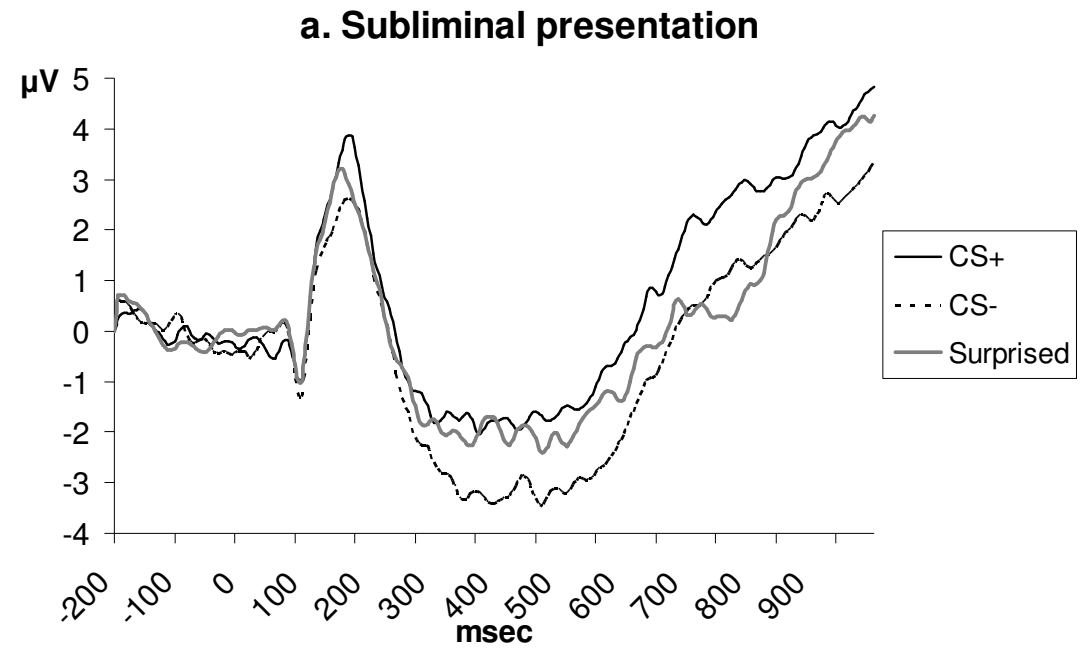
7.3.5 Data analysis

After visual inspection of the data, peak latencies and mean amplitudes were calculated per experimental block and electrode position, using BrainVision© semi-automatic peak detection. All data were analysed with SPSS 11.01 for Windows. Separate analyses were performed for subliminal and supraliminal presentation. In the analysis for subliminal presentation, the three stimulus conditions with a surprised mask were compared (condition 1, 2 and 5). In the analysis for supraliminal presentation, the three stimulus conditions with a surprised masked stimulus but with different masks were compared (condition 3, 4 and 5). Each analysis consisted of a GLM repeated measures (RM) ANOVA with the factors stimulus type (3 levels) and laterality (2 levels). Tests of within-subject contrasts were performed for the Surprised versus CS- stimuli and the CS+ versus CS- stimuli. Bonferroni correction for multiple comparisons was used for post-hoc analysis of effects.

7.4 ERP data

7.4.1 Visual inspection of the data

After visual inspection of the ERPs, three distinct electrophysiological events could be distinguished. The first component was P170, culminating at the frontal and central electrodes F3, Fz, F4, C3, Cz and C4. The second component was N280, culminating at the temporal electrodes T3 and T4. The third component was a Late Negativity (LN) which extended from 300 to 500 ms after stimulus presentation and culminates at prefrontal and frontal electrodes Fp1, Fp2, F3, Fz and F4. Grand averaged ERPs to the frontocentral electrode sites are displayed in Figure 7.3.



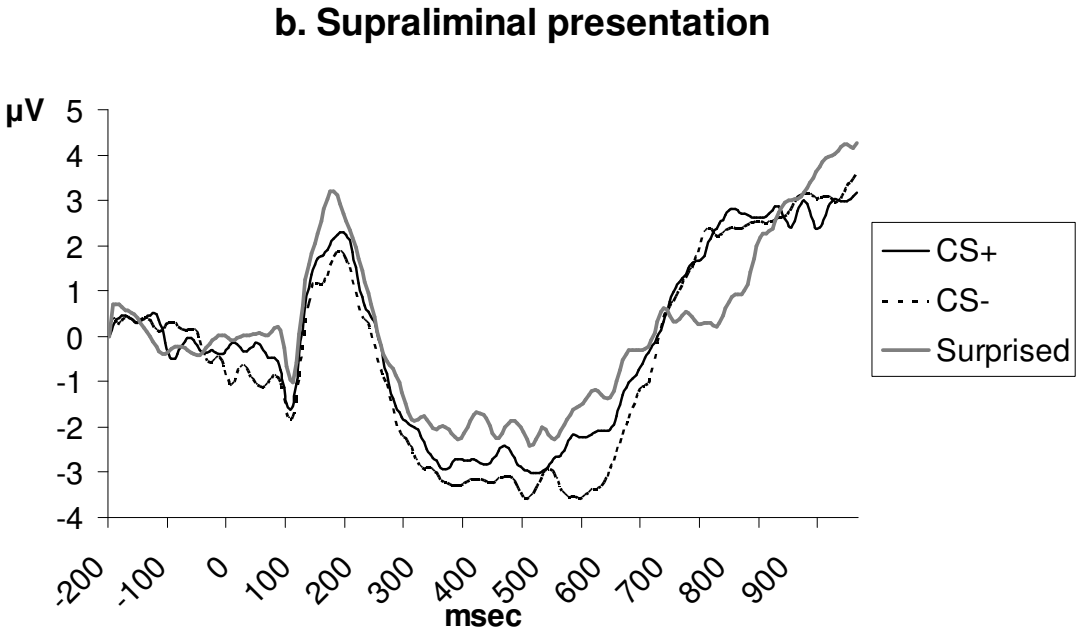


Figure 7.3. Grand averaged ERPs elicited at the frontocentral sites (Fp1, Fp2, F3, Fz, F4, C3, Cz and C4) to subliminal presentation (**a.**) and supraliminal presentation (**b.**) of three types of faces: Conditioned fearful face (CS+), Unconditioned fearful face (CS-) and Surprised face.

7.4.2 Calculation of ERP components

For every experimental block (22 in total), the mean ERPs were calculated for all five stimulus conditions. Mean latencies and amplitudes of the P170 and N280 were calculated with the use of the semi-automatic peak detection function in BrianVision© Analyser. For the Late Negativity, the mean amplitudes of the epoch 300-500 ms were calculated. Further data analysis was performed with SPSS 11.01 for Windows.

7.4.3 Statistical Analysis and Contrasts

For each ERP component, two separate analyses were performed: one for the subliminal presentation of the three types of stimuli (Fearful CS+, Fearful CS- and Surprised) and one for supraliminal presentation of these three types of stimuli. In the analysis for subliminal presentation, the three stimulus conditions with a surprised mask were compared (conditions 1, 2 and 5). In the analysis for supraliminal presentation, the three stimulus conditions with a surprised masked stimulus but with different masks were compared (conditions 3, 4 and 5). Each statistical analysis consisted of a GLM repeated measures (RM) ANOVA with the factors stimulus type (CS+, CS- and Surprised) and laterality (left and right electrode). Tests of within-subject contrasts were performed for the Surprised v CS- stimuli and the CS+ v CS- stimuli. Bonferroni correction for multiple comparisons was used for post-hoc analysis of effects.

Within each analysis thus, two contrasts were of importance. First the difference between the CS- and Surprised face, which can be interpreted as an effect of basic emotional expression. Second the contrast between CS- and CS+, which can be interpreted as an effect of classical averse conditioning. Results of the ERP analysis are summarized in Table 7.2.

7.4.4 Subliminal Presentation

7.4.4.1 P170

Two separate ANOVAs were executed for frontal (F3 and F4) and central electrodes (C3, C4) respectively.

Frontal electrodes: ANOVA revealed no main effect of Stimulus, but only for Lateralization ($F(1,21) = 11.17$, $p = 0.003$), caused by larger left-hemisphere P170

Table 7.2. Summary of results of the GLM Repeated Measures ANOVA. (Please note the following legend: + = $p < 0.1$; * = $p \leq 0.05$; ** = $p \leq 0.01$)

Component	Electrode Site	Basic Emotion Recognition (Surprised vs. CS-)	Conditioning (CS+ vs. CS-)
Subliminal			
P170	F3 – F4	n.s.	F(1,21) = 3.07 +
	C3 – C4	n.s.	F(1,21) = 8.14 *
Late Negativity	Fp1 – Fp2	F(1,21) = 11.52 **	F(1,21) = 7.83 *
	F3 – F4	F(1,21) = 3.28 +	F(1,21) = 12.12 **
Supraliminal			
P170	F3 – F4	F(1,21) = 6.70 *	n.s.
	C3 – C4	F(1,21) = 5.93 *	n.s.
Late Negativity	Fp1 – Fp2	F(1,21) = 3.97 +	n.s.
	F3 – F4	F(1,21) = 5.26 *	n.s.

amplitudes. There was no Stimulus x Lateralization interaction effect. Test of within-subject contrast showed a trend for the contrast related to aversive conditioning ($F(1,21) = 3.07$, $p = 0.094$), but in Bonferroni corrected post-hoc tests, mean CS+ amplitude was not significantly larger than CS- amplitude ($p > 0.20$).

Central electrodes: For the central electrodes, significant main effects for Stimulus ($F(2.42) = 5.74$, $p = 0.006$) as well as Lateralization ($F(1,21) = 38.39$, $p < 0.001$) were found. Left-hemisphere P170 amplitudes were larger than those in the right hemisphere. Within-subject contrasts showed a significant conditioning-related effect (CS+ vs. CS-; $F(1,21) = 8.14$, $p = 0.01$), but no effect of basic emotional expression (Surprised vs. CS-). Bonferroni corrected post-hoc tests showed that P170 amplitudes to CS+ stimuli were significantly larger than CS- ($p = 0.03$), and marginally larger than Surprised ($p = 0.055$).

7.4.4.2 N280

ANOVA showed a strong main effect for Lateralization (T3 and T4; $F(1,21) = 33.08$, $p < 0.001$), such that N280 amplitudes in the right hemisphere were larger (i.e. more negative) than left-hemisphere amplitudes. There was no main effect for Stimulus (CS+, CS- and Surprised).

7.4.4.3 Late Negativity

Two separate ANOVAs were performed for prefrontal (Fp1 and Fp2) and frontal (F3 and F4) electrodes respectively.

Prefrontal electrodes: ANOVA revealed a main effect for Stimulus ($F(2,42) = 5.34$, $p = 0.009$) and for Lateralization ($F(1,21) = 4.55$, $p = 0.045$), such that mean LN amplitudes in the right hemisphere were larger (i.e. more negative) than those in the left hemisphere. Within-subject contrasts showed an effect of conditioning ($F(1,21) = 7.83$, $p = 0.011$) and an effect of basic emotional expression ($F(1,21) = 11.52$, $p = 0.003$). Post-hoc comparisons showed that mean LN amplitudes to CS- were larger (i.e. more negative) than LN amplitudes to CS+ and Surprised amplitudes (all $p < 0.05$; Bonferroni corrected).

Frontal electrodes: A main effect of Stimulus ($F(2,42) = 5.51$, $p = 0.008$) as well as for Lateralization ($F(1,21) = 55.14$, $p < 0.001$) was found. The effect of Lateralization was due to larger (i.e. more negative) mean LN amplitudes in the right hemisphere compared to the left hemisphere. Tests of within-subject contrasts showed a significant conditioning-related effect ($F(1,21) = 12.12$, $p = 0.002$) and a trend for the basic emotion-related effect ($F(1,21) = 3.28$, $p = 0.085$). Post-hoc tests revealed larger (i.e. more negative) mean LN amplitudes to the CS- compared to CS+ ($p = 0.005$; Bonferroni corrected), but no significant differences between Surprised and CS-.

7.4.5 Supraliminal presentation

7.4.5.1 P170

Separate ANOVAs were carried out for the frontal electrodes (F3 and F4) and the central electrodes (C3 and C4) respectively.

Frontal electrodes: There was a main effect of Stimulus ($F(2, 42) = 3.68$, $p = 0.034$) and also an main effect of Lateralization ($F(1,21) = 10.85$, $p = 0.003$), due to higher P170 amplitudes in the left hemisphere compared to the right hemisphere. There was

no interaction effect of Stimulus x Lateralization. Within-subject contrasts showed an effect of basic emotional expression ($F(1,21) = 6.70$, $p = 0.017$), but not for aversive conditioning. Post-hoc Bonferroni corrected comparisons showed a strong trend for P170 amplitude to Surprised faces being larger than P170 amplitudes to CS- ($p = 0.052$). Other comparisons were not significant.

Central electrodes: ANOVA showed a trend for an effect of Stimulus ($F(2,42) = 2.79$, $p = 0.074$), and an effect of Lateralization ($F(1,21) = 40.81$, $p < 0.001$), with left-hemisphere P170 amplitudes being larger than right-hemisphere amplitudes. There was no significant Stimulus x Lateralization interaction effect. Within-subject contrasts showed an effect of basic emotional expression ($F(1,21) = 5.93$, $p = 0.024$), but no effect of aversive conditioning. Post-hoc comparisons only showed a trend for P170 amplitudes to Surprised stimuli being larger than CS- ($p = 0.072$; Bonferroni corrected).

7.4.5.2 N280

Repeated measures ANOVA with Stimulus (CS+, CS- and Surprised) and Lateralization (T3 and T4) as within-subject factors showed only a significant effect for Lateralization ($F(1,21) = 89.82$, $p < 0.001$), but no main effect for Stimulus or interaction effect for Stimulus x Lateralization. Mean N280 amplitudes in the right hemisphere were larger (i.e. more negative) than in the left hemisphere ($p < 0.001$; Bonferroni corrected).

7.4.5.3 Late Negativity

Separate analyses were carried out for the prefrontal electrodes (Fp1 and Fp2) and the frontal electrodes (F3 and F4) respectively.

Prefrontal electrodes: ANOVA showed a main effect for Lateralization ($F(1,21) = 7.26$, $p = 0.014$), but no main effect for Stimulus. Mean LN amplitudes in the right hemisphere being larger (i.e. more negative) than in the left hemisphere. No significant Stimulus x Lateralization interaction was found. Tests of within-subject contrasts showed a trend for the basic emotional expression-contrast ($F(1,21) = 3.97$, $p = 0.060$), but no effect related to the conditioning-related contrast. None of the post-hoc comparisons for Stimulus attained significance (all $p > 0.1$).

Frontal electrodes: There was a weak trend for a main effect of Stimulus ($F(2,42) = 2.58$, $p = 0.087$), and a strong main effect for Lateralization ($F(1,21) = 69.6$, $p <$

0.001) such that the LN amplitudes in the right hemisphere were the largest (i.e. more negative). No further Stimulus x Lateralization interaction was found. Tests of within-subject contrasts showed a significant effect of basic emotional expression ($F(1,21) = 5.26$, $p = 0.032$). However, in post-hoc comparisons only a marginal trend for larger (i.e. more negative) mean LN amplitudes for the CS- stimuli compared to Surprised could be established ($p = 0.094$; Bonferroni corrected).

7.4.6 Summary of Results

Three distinct electrophysiological events were analysed: P170, N280 and LN. On the P170 and LN components, an effect of stimulus was found. On the N280 only an effect of lateralization was found. The N280 will therefore not be discussed further.

With regard to the P170, a significant effect of classical conditioning was found under circumstances of subliminal presentation, while there was no effect of basic emotion recognition. P170 amplitudes to the masked CS+ stimulus were higher than to the masked CS- stimuli. However, this effect reversed under circumstances of supraliminal presentation. Under these circumstances, in which P170 amplitudes to three different types of mask were compared, no effect of classical conditioning was found, while the effect of basic emotion recognition was significant. P170 amplitudes to the Surprised faces were higher than those to CS- stimuli.

With regard to the LN, significant effects of classical conditioning and basic emotion recognition were found under circumstances of subliminal presentation. Mean LN amplitudes to the CS- were more negative compared to LN amplitudes to CS+ and Surprised stimuli. Under circumstances of supraliminal presentation, only an effect of basic emotion recognition was found. There was a trend for mean LN amplitudes to CS- being larger than to Surprised stimuli.

7.5 Discussion

7.5.1 Processing of Fear versus Surprise

Although FZ consistently mistakes fearful expressions for surprise, we tested whether these two emotional expressions would nevertheless give rise to different neuronal response patterns. Our data clearly shows that this is the case. Under circumstances of supraliminal presentation (i.e. conscious perception), P170 and LN amplitudes to the

CS- were different from P170 and LN amplitudes to the Surprised stimuli. It is therefore fair to conclude that in FZ's brain fearful and surprised emotional expressions are processed differently even though FZ is not able to report a difference between these two facial emotional expressions. This indicates that, in the absence of overt recognition of fearful facial expressions, some level of covert recognition still exists.

There might be several explanations for this discrepancy between FZ's ERP pattern and his reported perception. First, it could be the case that although ERPs indicate that FZ's brain registers a difference between fear and surprise, this difference is not significant enough to reach a certain threshold to *report* the difference. It would be interesting to investigate whether explicit (i.e. reported) discrimination between fearful and surprised expressions would improve if extreme caricatures of these two emotional expressions were used.

Second, one could speculate that the differences in ERPs to fearful and surprised faces only reflect the differences in facial configuration between these two emotions. Supposing this would be the case, FZ's brain successfully registered the configural differences between a fearful face and a surprised face but does not relate these differences to separate emotional expressions. In other words, although FZ might be able to 'see' that a fearful face is structurally different from a surprised face, he still reports they belong to the same emotion, namely surprise.

It has been shown that patients with cortical blindness can reliably discriminate facial emotional expressions even if they are unaware of their percept (De Gelder et al., 1999; Pegna et al., 2005b). This ability is also referred to as 'affective blindsight'. Using fMRI, Pegna et al.(Pegna et al., 2005a) showed that, in a patient with a lesion of the bilateral primary visual areas, the right amygdala was still responding differentially to the emotional expressions of anger, fear and happiness compared to neutral faces. Like Pegna's patient, FZ has no explicit recognition of fear, while his brain is responding differentially to different emotion expressions (i.e. fear and surprise). This implies that at least some degree of covert, implicit, recognition of fear is still intact. However, while Pegna's patient was cortically blind but used the right amygdala for implicit emotional recognition, our patient FZ has no occipital blindness but a damaged right amygdale.

Studies of affective blindsight thus have shown that an undamaged right amygdale with a damaged striate cortex may be sufficient for implicit emotional

processing, whereas our study shows that a reversed pattern of brain damage may be sufficient for implicit emotion recognition as well. Our study also indicates that the right hemisphere may play a crucial role in the explicit processing of fear - a function that, at least in FZ, cannot be compensated for by the left hemisphere.

7.5.2 Conscious versus unconscious processing of conditioned stimuli

We investigated conscious versus unconscious processing of aversively conditioned stimuli in FZ. It is clear from our data that despite FZ's inability to consciously recognize fear, aversive conditioning is still intact. Strikingly, we only found an effect of conditioning under circumstances of subliminal presentation. In an imaging study with healthy subjects, Morris at al (1998) found left amygdala responses to seen CS+ and right amygdala responses to unseen CS+. Since FZ has a lesion of the right amygdala, we would have expected to find differences in ERPs to CS- and CS+ under circumstances of supraliminal presentation, but not under circumstances of subliminal presentation. Taking into account that the process of aversive conditioning itself took place under circumstances of supraliminal presentation, this finding is even more striking. Our results suggest that the right amygdala is not necessary for aversive conditioning, even when explicit recognition of fear is absent.

Aversive conditioning is a process in which the amygdala is thought to play a crucial role, and for which processing by cortical brain structures is not necessary. Several studies have shown that patients with lesions of the cortical visual areas may still have intact fear conditioning (Hamm et al., 2003; Morris et al., 2001). Hamm et al. (2003) found that a cortically blind patient with bilateral occipital lesions was able to acquire a fear conditioned startle response to an unseen visual cue. In an fMRI experiment, Morris et al. (2001) showed that in their patient GY with homonymous hemianopia, aversively conditioned faces that were presented in the blind hemifield still elicited amygdala responses. In that study, GY showed bilateral amygdala activity to the unseen CS+, of which the right amygdala responses were more spatially extensive. The right amygdala may thus be sufficient to allow aversively conditioning, even in the absence of visual processing via the primary visual cortex. Our study with patient FZ shows that intact right amygdala function is not necessary for aversive conditioning.

In our study, the effects of aversive conditioning only occurred under circumstances of subliminal presentation. The absence of this effect under

circumstances of supraliminal presentation could be an indication that cortical processing is dominant over subcortical processing. This inhibition or overruling of subcortical processing is no longer possible when stimuli are presented outside the scope of conscious awareness.

Previous studies with healthy subjects and cortically blind patients have stressed the importance of the right amygdala for discriminating facial emotional expressions and for classical conditioning. Our study suggests that the right amygdala is indeed necessary for overt, explicit, discrimination of fear, while covert, implicit, discrimination of fear and classical conditioning may still occur without the right amygdala.

Acknowledgement

The authors thank Joop Clots and Jan Smit for their technical support, and Céline Crajé for her help with the data acquisition.

References

Adolphs, R., Baron-Cohen, S., & Tranel, D. (2002). Impaired recognition of social emotions following amygdala damage. *Journal of Cognitive Neuroscience, 14,* 1264-1274.

Adolphs, R. & Tranel, D. (2003). Amygdala damage impairs emotion recognition from scenes only when they contain facial expressions. *Neuropsychologia, 41,* 1281-1289.

Adolphs, R. & Tranel, D. (2004). Impaired judgments of sadness but not happiness following bilateral amygdala damage. *Journal of Cognitive Neuroscience, 16,* 453-462.

Adolphs, R., Tranel, D., & Damasio, A. R. (1998). The human amygdala in social judgement. *Nature, 393,* 470-474.

Adolphs, R., Tranel, D., Damasio, H., & Damasio, A. R. (1994). Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. *Nature, 372,* 669-672.

Adolphs, R., Tranel, D., Hamann, S., Young, A. W., Calder, A. J., Phelps, E. A. et al. (1999). Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia, 37,* 1111-1117.

Amaral, D. G., Price, J. L., Pitkänen, A., & Carmichael, S. T. (1992). Anatomical organization of the primate amygdaloid complex. In J.P.Aggleton (Ed.), *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction* (pp. 1-66). New York: Wiley-Liss.

Anderson, A. K., Spencer, D. D., Fulbright, R. K., & Phelps, E. A. (2000). Contribution of the anteromedial temporal lobes to the evaluation of facial emotion. *Neuropsychology., 14,* 526-536.

Bauer, R. M. (1984). Autonomic recognition of names and faces in prosopagnosia: a neuropsychological application of the Guilty Knowledge Test. *Neuropsychologia, 22,* 457-469.

Benton, A. L., Hamsher, K. d., Varney, N. R., & Spreen, O. (1983a). *Contributions to neuropsychological assessment. A clinical manual*. Oxford: Oxford University Press.

Benton, A. L., Hamsher, K. d., Varney, N. R., & Spreen, O. (1983b). *Facial Recognition. Stimulus and Multiple Choice Pictures*. Oxford: Oxford University Press.

Buchanan, T. W., Denburg, N. L., Tranel, D., & Adolphs, R. (2001). Verbal and nonverbal emotional memory following unilateral amygdala damage. *Learning and Memory, 8,* 326-335.

Damasio, A. R. (1985). Prosopagnosia. *Trends in Neurosciences, 8,* 132-135.

Davidson, R. J. & Irwin, W. (1999). The functional neuroanatomy of emotion and affective style. *Trends in Cognitive Sciences, 3,* 11-21.

De Gelder, B., Vroomen, J., Pourtois, G., & Weiskrantz, L. (1999). Non-conscious recognition of affect in the absence of striate cortex. *Neuroreport, 10,* 3759-3763.

De Haan, E. H. F., Young, A., & Newcombe, F. (1987). Face Recognition Without Awareness. *Cognitive Neuropsychology, 4,* 385-415.

De Haan, E. H. F., Young, A. W., & Newcombe, F. (1991). Covert and overt recognition in prosopagnosia. *Brain, 114 (Pt 6),* 2575-2591.

Diesfeldt, H. & Vink, M. (1989). Recognition memory for words and faces in the very old. *British Journal of Clinical Psychology, 28 (Pt 3),* 247-253.

Doron, N. N. & LeDoux, J. E. (1999). Organization of projections to the lateral amygdala from auditory and visual areas of the thalamus in the rat. *Journal of Computational Neurology, 412,* 383-409.

Ekman, P. & Friesen, W. V. (1976). *Pictures of Facial Affect*. Palo Alto: Consulting Psychologists Press.

Frank, J. E. & Tomaz, C. (2003). Lateralized impairments of the emotional enhancement of verbal meomory in patients with amygdala-hippocampus lesion. *Brain and Cognition, 52,* 223-230.

Funayama, E. S., Grillon, C., Davis, M., & Phelps, E. A. (2001). A double dissociation in the affective modulation of startle in humans: effects of unilateral temporal lobectomy. *Journal of Cognitive Neuroscience, 13,* 721-729.

Gauthier, L., Dehaut, F., & Joannette, Y. (1989). The bells test: a quantitative and qualitative test for visual neglect. *International Journal of Clinical Neurosychology, 11,* 49-54.

Gratton, G., Coles, M. G. H., & Donchin, E. (1983). A new method for off-line removal of ocular artefact. *Electroencephalography and Clinical Neurophysiology, 55,* 468-484.

Hamm, A. O., Weike, A. I., Schupp, H. T., Treig, T., Dressel, A., & Kessler, C. (2003). Affective blindsight: intact fear conditioning to a visual cue in a cortically blind patient. *Brain, 126,* 267-275.

Keightley, M. L., Winocur, G., Graham, S. J., Mayberg, H. S., Hevenor, S. J., & Grady, C. L. (2003). An fMRI study investigating cognitive modulation of brain regions associated with emotional processing of visual stimuli. *Neuropsychologia, 41,* 585-596.

LaBar, K. S., LeDoux, J. E., Spencer, D. D., & Phelps, E. A. (1995). Impaired fear conditioning following unilateral temporal lobectomy in humans. *Journal of Neuroscience, 15,* 6846-6855.

LeDoux, J. E. (1993). Emotional memory systems in the brain. *Behavioural Brain Research, 58,* 69-79.

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience, 23,* 155-184.

LeDoux, J. E., Sakaguchi, A., & Reis, D. J. (1984). Subcortical efferent projections of the medial geniculate nucleus mediate emotional responses conditioned to acoustic stimuli. *Journal of Neuroscience, 4,* 683-698.

Luteijn, F. & Van der Ploeg, F. A. E. (1983). *Handleiding GIT*. Lisse: Swets & Zeitlinger.

Mazurski, E. J., Bond, N. W., Siddle, D. A. T., & Lovibond, P. F. (1996). Conditioning with facial expressions of emotion: effects of CS sex and age. *Psychophysiology, 33,* 416-425.

Morris, J. S., DeGelder, B., Weiskrantz, L., & Dolan, R. J. (2001). Differential extrageniculostriate and amygdala responses to presentation of emotional faces in a cortically blind field. *Brain, 124,* 1241-1252.

Morris, J. S., Öhman, A., & Dolan, R. J. (1998). Conscious and unconscious emotional learning in the human amygdala. *Nature, 393,* 467-470.

Pegna, A. J., Khateb, A., Lazeyras, F., & Seghier, M. L. (2005b). Discriminating emotional faces without primary visual cortices involves the right amygdala. *Nature Neuroscience, 8,* 24-25.

Pegna, A. J., Khateb, A., Lazeyras, F., & Seghier, M. L. (2005a). Discriminating emotional faces without primary visual cortices involves the right amygdala. *Nature Neuroscience, 8,* 24-25.

Reitan, R. M. (1955). The relation of the trail making test to organic brain damage. *Journal of Consulting and Clinical Psychology, 19,* 393-394.

Renault, B., Signoret, J. L., Debruille, B., Breton, F., & Bolgert, F. (1989). Brain Potentials Reveal Covert Facial Recognition in Prosopagnosia. *Neuropsychologia, 27,* 905-912.

Saan, R. J. & Deelman, B. G. (1986). *De 15-Woorden Tests A en B (Een voorlopige handleiding)*. Groningen: Dept. Neuropsychology, AZG (internal publication).

Schmand, B. & De Koning, I. (2003). *Trailmaking Test A en B. Toelichting bij afname en normen*. Amsterdam: Nederlands Instituut voor Psychologen, sectie Neuropsychologie.

Schmand, B., Houx, P., & De Koning, I. (2003). *Stroop kleur-woord test. Toelichting bij afname en normen*. Amsterdam: Nederlands Instituut voor Psychologen, afdeling Neuropsychologie.

Schmolck, H. & Squire, L. R. (2001). Impaired perception of facial emotions following bilateral damage to the anterior temporal lobe. *Neuropsychology., 15,* 30-38.

Scott, S. K., Young, A. W., Calder, A. W., Hellawell, D. J., Aggleton, J. P., & Johnson, M. (1997). Impaired auditory recognition of fear and anger following bilateral amygdala lesions. *Nature, 385,* 254-257.

Towle, D. & Lincoln, N. (1991). Development of a questionnaire for detecting everyday problems in stroke patients with unilateral neglect. *Clinical Rehabilitation, 5,* 135-140.

Tranel, D. & Damasio, A. R. (1988). Non-conscious face recognition in patients with face agnosia. *Behavioural Brain Research, 30,* 235-249.

Tranel, D., Damasio, H., & Damasio, A. R. (1995). Double Dissociation Between Overt and Covert Face Recognition. *Journal of Cognitive Neuroscience, 7,* 425-432.

Van de Berg, Y., Diesfeldt, H. F. A., Saan, R. J., & Eling, P. (1995). *Herkenningstest voor Woorden en Gezichten. Een normeringsonderzoek*. Nijmegen: KUN (internal report).

van Zomeren, A. H. & Deelman, B. G. (1978). Long-Term Recovery of Visual Reaction-Time After Closed Head-Injury. *Journal of Neurology Neurosurgery and Psychiatry, 41,* 452-457.

Wang, K., Hoosain, R., Yang, R. M., Meng, Y., & Wang, C. Q. (2003). Impairment of recognition of disgust in Chinese with Huntington's or Wilson's disease. *Neuropsychologia, 41,* 527-537.

Warrington, E. K. (1984). *Recognition Memory Test*. Windsor: NFER-Nelson.

Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., & Jenike, M. A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *Journal of Neuroscience, 18,* 411-418.

Young, A., Perrett, D. I., Calder, A. J., Sprengelmeyer, R., & Ekman, P. (2002). *Facial Expression of Emotion - Stimuli and Tests (FEEST)*. Bury St. Edmunds: Thames Valley Test Company.

Zald, D. H. (2003). The human amygdala and the emotional evaluation of sensory stimuli. *Brain Research Reviews, 41,* 88-123.

Zimmerman, P. & Fimm, B. (1996). Testbatterij voor Aandachtsprestaties (TAP) [Computer software]. Wurselen: Vera Fimm / Psychologische Testsysteme.

Chapter 8

Summary

The main focus of this thesis was to study the interactions between visual processing streams and, more specifically, covert and overt visual processing via these streams. Section 1 of this thesis provided an overview of the brain structures involved in visual processing. In section 2, rehabilitation methods for homonymous hemianopia and unilateral neglect were reviewed. Section 3 consisted of three experimental studies in which covert and overt processing of faces, emotional facial expressions and conditioned faces were studied. In this chapter, the main findings of the previous chapters will be summarized.

In *chapter 2*, three parallel visual processing streams were described: a dorsal, occipitoparietal stream for processing visual information related to movement, location and motor action; a ventral, occipitotemporal stream for processing information related to specialized recognition of objects and faces; and a subcortical, cortico-amygdalar and thalamo-amygdalar pathway for processing of emotion-related information.

Impaired visual perception may occur as a result of brain damage. Different types of impaired visual perception were described, that could be related to damage of a distinct stage of visual processing or a distinct visual processing stream. Damage to the lateral geniculate nucleus, the optic radiation or the extrastriate cortex leads to homonymous field defects. Unilateral neglect and Bálint syndrome were described as examples of perceptual disorders after damage to the dorsal stream. Damage to the ventral stream may lead to agnosias. Two specific agnosias were described in the introduction: pure alexia and prosopagnosia. Damage to the amygdala, which is a crucial brain structure for visual processing of emotion-related information, may lead to impaired recognition of negative emotional facial expressions, such as fear.

Although each stream is primarily dedicated to a specific category of visual information, this does not mean that this category is processed exclusively by a single stream. First, many interactions exist between the streams to allow purposeful behaviour, such as visuomotor actions or complex social behaviour. Second, the visual processing streams are capable of modulating each other, either in a top-down or in a bottom-up fashion. Third, impaired processing of a specific category of visual information may in some cases be overcome by processing via another stream, which is not the primary designated stream for that specific type of information. Fourth, visual processing via a not-primarily designated stream may in some cases lead to so-

called ‘covert’ processing – as opposed to ‘overt’ processing via the primarily designated visual processing route.

In section 2, rehabilitation methods for two common visual impairments after acquired brain damage were reviewed. *Chapter 3* consisted of a systematic review of the two main rehabilitation methods for patients with homonymous visual field defects (HVFDs): vision restoration therapy (VRT) and scanning compensatory therapy (SCT).

In general, the effect of VRT was only evaluated in terms of the increase of visual field size. Since the basic assumption of VRT is that this increase of the visual field size will help patients with HVFDs to improve functions related to reading and mobility (e.g. better reading performance and less bumping into objects), tasks related to these functions should have been included in the outcome measures. While the evidence for the effect of VRT leans heavily on a change of visual field size, which is also called ‘border shift’, the very techniques aiming to reliably assess this border shift have been questioned. It was therefore concluded that the effects of VRT remain unclear until general consensus is reached which methods of perimetry should be used to measure the exact size of the visual field and the alleged improvements in the transition zone. The recommended treatment for patients with HVFDs is SCT. However, the current body of evidence for SCT should be further substantiated by randomized controlled trials.

Chapter 4 consisted of a review of rehabilitation methods aiming to improve unilateral neglect. In many respects, patients suffering from the neglect syndrome form a heterogeneous group and this complicates the decision which rehabilitation method should be generally recommended. First of all, neglect symptoms cannot be linked to a single, discrete anatomical structure. In most patients, neglect appears to be caused by right hemisphere lesions including the temporoparietal-occiptital junction. However, other regions, such as the thalamus, the middle temporal lobe, and the superior temporal lobe may also cause neglect. Also, the symptoms of neglect may vary from patient to patient. For instance, some patients may be more impaired at motor tasks, while others may be more impaired at sensory tasks. Neglect patients may have non-lateralized attentional deficits, such as impaired arousal and impaired sustained attention, which also interact with the neglect symptoms.

Whatever the origin and nature, the neglect syndrome can be regarded as a disorder of impaired dorsal processing. While some rehabilitation methods aim at learning patients to overcome their deficits by applying compensation strategies, as is the case in visual scanning therapy, other interventions aim to use intact networks to modulate or even restore the impaired network. It was concluded that the effects of intensive compensatory training appear to mainly limited to the tasks that are trained. The effects of some of the interventions that aim to overcome the underlying deficits, for example caloric stimulation by pouring iced water in the left ear canal, appear to be compelling. Nevertheless, their effects are also very short-lived.

In section 3, three experimental studies were presented that focused on covert and overt processing of faces or emotional facial expressions. In *chapter 5*, a patient (JS) was described, who displayed symptoms of both prosopagnosia and Capgras delusion. JS had impaired recognition of familiar faces, which is the hallmark of prosopagnosia. However, recognition of close family members was far worse than recognition of celebrities. Moreover, JS had delusional attributions about the appearance of people with whom recognition was accompanied by a strong emotional connotation. For instance, JS believed that her grandchildren looked extremely tanned and corpulent. The fact that that recognition of close family members was more impaired than recognition of celebrities, and that recognition of family members was accompanied by a delusional attribution, provides some striking similarities with Capgras delusion. On the other hand, patients suffering from Capgras delusion normally have adequate performance on face recognition tasks.

To explore this phenomenon, different measures of covert and overt face recognition were employed to assess performance on a face recognition tasks. JS' performance was compared with three control subjects who were matched for age, sex and family size. Whereas control subjects had faster decision times for recognizing photographs of family members compared to celebrities and unfamiliar people, JS showed an opposite pattern, as her decision times for recognition of family member was almost twice as long as for celebrities and unfamiliar people. Strikingly, JS' had enhanced skin conductance responses (SCRs) to presentation of images of family members, compared to unfamiliar people. This may indicate that, in the absence of overt face recognition, some type of covert face processing is still intact, although it was argued that the enhanced SCRs may be indicative of other mechanisms as well.

A second experimental study, designed to investigate early, pre-attentive visual processing of facial emotional expressions and aversively conditioned faces, was described in *chapter 6*. In this study, event-related potentials (ERPs) to masked and unmasked photographs of faces were assessed in 32 young adults. Two early ERP components were analysed: P1 and N170. The P1 component is related to extrastriate activity and is usually considered to be the first endogenous ERP component in visual processing, but in some studies P1 has been shown to be sensitive to face processing as well. The N170 is regarded as the first face-specific ERP component and has been linked with the phase of structural encoding, during which facial features are integrated to generate a face representation. In the experiment described in this chapter, face stimuli consisted of a neutral face (N), an unconditioned angry face (CS-) or an aversively conditioned angry face (CS+). Stimuli were presented either masked, to assess visual processing without awareness, or unmasked, to assess conscious processing.

P1 was only sensitive to masked presentation of stimuli. P1 amplitudes to CS- masked faces were higher than those elicited by masked CS+ and N stimuli, while P1 amplitudes to masked CS+ stimuli were lower than masked N stimuli. N170 amplitudes were sensitive to conditioning when stimuli were masked: amplitudes to CS+ were less negative than CS- amplitudes. In the unmasked condition, N170 was only sensitive to facial emotional expression: amplitudes to N stimuli were more negative than CS- amplitudes.

Interestingly, P1 amplitudes in the masked condition interacted with subjects' experienced anxiety in daily life, as assessed by the State-Trait Anxiety Inventory. Subjects with relatively high trait anxiety had higher P1 amplitudes in general and, more specifically, showed no difference between P1 amplitudes to CS+ and N. Whereas trait anxiety only correlated with P1 amplitudes, state anxiety only correlated with N170 amplitudes. Subjects with low state anxiety had more negative N170 amplitudes than subjects with high state anxiety.

It was concluded that P1 and N170 may reflect distinct neural mechanisms of face processing. P1 may be sensitive to unconscious processing of both facial emotional expression and classical conditioning. N170 may be sensitive to unconscious processing of conditioning and conscious processing of emotional facial expressions. It was argued that the P1 modulation may reflect afferent projections of

the amygdala to the extrastriate cortex. N170 may reflect afferent projections of the amygdala to later stages of cortical processing.

In *chapter 7*, a patient (FZ) was described, who had impaired overt recognition of fear after a lesion of the right lower and middle temporal gyrus and the right amygdala. Employing ERPs in a backward masking design similar to the one described in chapter 6, covert processing of facial emotional expressions and aversively conditioned faces was assessed. Stimuli consisted of faces with a surprised emotional facial expression (S), an unconditioned fearful face (CS-) and an aversively conditioned fearful face (CS+). Two ERP components could be related to the experimental manipulation: a centrofrontal P170 and a frontal Late Negativity. P170 was only sensitive to the effect of aversive conditioning (i.e. the difference between CS- and CS+) when these stimuli were presented in the unmasked condition. However, in the masked condition, N170 was only sensitive to the effect of basic emotional expression (i.e. the difference between S and CS-). The frontal Late Negativity component was sensitive to the effect of aversive conditioning and basic emotional expression in the masked condition, and only sensitive to the effect of basic emotional expression in the unmasked condition.

It was concluded that, although FZ has no explicit recognition of fearful facial expressions, the ERP data in this experiment show that, at least to a certain extent, covert processing of fear is still intact. The fact that an effect of aversive conditioning was only found under circumstances of masked presentation, might be indicative of the involvement of the intact left amygdala in this type of visual processing.

Chapter 9

General discussion and conclusion

9.1 Interactions between visual processing streams

In the introduction of this thesis, three parallel and interacting pathways or streams for visual processing were described, namely dorsal, ventral and subcortical. Although each stream is primarily designated to process a distinct category of visual information, many reciprocal connections exist between these streams. It was illustrated that in a healthy brain, these interactions are required to allow complex behaviour, such adequate responses to emotionally significant information. Also, in the introduction section and in the review of neglect rehabilitation, several examples were given how interactions between the visual processing streams may help to overcome impaired visual processing, for instance via joint activation of mutually facilitatory networks.

The main focus of the experimental studies in this thesis was on the interaction between the subcortical and ventral streams in processing face-related information. Faces bear a wide range of important information, such as gender, familiarity and emotional expressions. The model proposed by Bruce and Young (Bruce & Young, 1986), described in *chapter 4*, shows how face recognition and emotion analysis may occur via successive stages in a highly specialized ventral stream. According to this model, both the recognition of faces and the analysis of emotional expression take place after an initial stage of structural encoding. In evoked response potential (ERP) studies, this stage of structural encoding has been linked with the N170 component (Eimer, 2000a; Eimer, 2000b; Eimer & Holmes, 2002; Holmes et al., 2003).

There is ample evidence that the amygdala is involved in processing of negative facial emotional expressions, most specifically fear and anger (Adolphs et al., 1999; Adolphs & Tranel, 2004; Calder et al., 1996; Morris et al., 1996; Scott et al., 1997). LeDoux provided an elegant model, in which processing of emotional information is supported by two routes or 'roads' (LeDoux, 1996; LeDoux, 2002). According to this model, the 'low road' allows extremely fast processing of emotional information via a direct projection of the thalamus to the amygdala. When processing occurs via the 'high road', the amygdala receives input from the sensory cortex. The 'low road' is thought to be 'quick and dirty', due to the crude representations of visual information in the thalamus, while the 'high road' is thought to be 'slow but accurate', since detailed, high level input from the sensory cortex is preceded by numerous processing stages. Applying this model to the processing of emotional facial

expressions, the 'high road' is constituted of highly specialized processing via the ventral stream.

The results of the ERP study of emotional processing in healthy subjects, presented in *chapter 6*, showed a modulation of the early P1 component dependent on facial emotional expression. It is unlikely that this effect reflects emotional processing via the ventral route, since the phase of structural encoding, which is thought to occur before emotion analysis, occurs at a later point in time. It appears more likely that this P1 modulation reflects subcortical emotional processing. However, in LeDoux' proposed 'low road', direct processing via the thalamus and amygdala bypasses the cortex, while the P1 is linked with extrastriate activity (Foxe & Simpson, 2002; Heinze et al., 1994). The results may therefore provide evidence that preattentive emotional processing via the subcortical route can modulate activity in the visual cortex via afferent projections from subcortical structures towards early stages of the ventral stream.

The modulation of the P1 component was not only dependent on facial emotional expression. The results also showed an effect of classical conditioning on P1. Remember that in this experiment two different angry faces were presented, one of which was previously paired with a loud noise, while the other angry face was never paired with this noise. As was mentioned earlier, processing via the 'low road' is thought to be 'quick and dirty' due to the crudeness of representations of visual information in the thalamus. But how crude are these representations? Based on the results of this ERP study, subcortical processing not only allowed discrimination between two categories of emotional facial expressions (i.e. neutral and angry), but it also allowed discrimination between two angry faces: one conditioned and one unconditioned. It has been suggested that fast processing of emotional information via the subcortical route may lead to an overgeneralization of responses (Zald, 2003). The fact that P1 was sensitive to differences between facial emotional expressions and to differences within the same emotional expression suggests that the modulation of the visual cortex via afferent projections of the subcortical stream did not suffer from this overgeneralization. Hence, subcortical structures might be capable of more detailed visual processing then previously thought. However, in subjects with high trait anxiety, indicative of neuroticism, the modulation of P1 was less specific than in subjects with low trait anxiety. This indicates that people with high trait anxiety are

more vulnerable to this overgeneralization of fear resonse than people with low trait anxiety. This subject will be discussed further in a later paragraph.

Both ERP experiments presented in this thesis (*chapters 6 and 7*) indicate that ERPs to masked stimuli and unmasked stimuli reflect processing via different routes. It has been suggested that processing of aversively conditioned stimuli may occur via thalamo-amygdalar processing without the need of cortical involvement (Doron & LeDoux, 1999; LeDoux et al., 1984; Morris et al., 1998; Morris et al., 1999). In the ERP study with FZ and the study with healthy subjects, a conditioning-dependent modulation was only found when stimuli were presented outside the scope of awareness, namely when stimuli were masked. This is in line with other studies suggesting that thalamo-amygdalar processing is particularly linked with masked presentation of emotional stimuli (Morris et al., 1999; Whalen et al., 1998). The effects found in both ERP studies when stimuli were supraliminally presented may very well reflect cortical processing via the ventral route, since no effect of conditioning was found under these circumstances.

The question can be raised which subcortical brain structures are involved in the emotion-dependent preattentive modulation of the visual cortex that was indicated by the modulation of P1 in the experiment with healthy subjects. As the amygdala is located anterior within the medial temporal lobes, is it not possible to assess amygdala activity directly via ERP measures, since the electrodes are positioned on the surface of the skull. Nevertheless, the study with FZ provides indirect evidence for the involvement of the amygdala. In ERPs of healthy subjects, both an effect of facial emotional expression and of conditioning was found to masked presentation of stimuli. In FZ however, who has a right amygdala lesion, only the effect of conditioning was found to masked presentations, and no effect of emotional expression. This indicates that the right amygdala plays a crucial role in the modulation of the visual cortex by subcortical processing of facial emotional expression.

In the previous paragraphs, it was argued that subcortical visual processing modulates the visual cortex in response to facial expressions and aversively conditioned faces. In this paragraph, the nature of this interaction between subcortical and cortical visual processing will be discussed further. Early, emotion dependent modulation of the visual cortex have been found by other authors as well (Batty & Taylor, 2003; Pizzagalli et al., 1999; Schupp et al., 2007; Streit et al., 1999; Streit et

al., 2000), and these findings have been interpreted in terms of a 'reflexive' selective attention process by which emotionally significant stimuli are selected for more elaborated processing (Sato et al., 2001; Schupp et al., 2000). In the ERP experiment described in *chapter 6*, P1 amplitudes to angry faces were larger than P1 amplitudes to neutral faces. As P1 amplitudes are larger to attended stimuli than to unattended stimuli (McDonald et al., 1999), this provides further evidence that cortical processing of emotionally relevant stimuli can be enhanced via afferent projections of subcortical brain structures. Moreover, in the same experiment, P1 amplitudes to conditioned angry faces were lower than P1 amplitudes to neutral faces and unconditioned angry faces. This implies that the same afferent projections are also capable of reducing cortical processing, indicating that the bottom-up modulatory role of subcortical visual processing on cortical processing may act in two ways, namely boosting selective attention and reducing selective attention.

But why would cortical processing of an unconditioned angry face be enhanced and cortical processing of a conditioned angry face be reduced? One might speculate that this reflects an efficient use of cortical processing capacity. As conditioned stimuli can be processed without the need of cortical involvement (Doron & LeDoux, 1999; LeDoux et al., 1984; Morris et al., 1998; Morris et al., 1999), the aversively conditioned face did not require cortical processing, hence selective attention was reduced to presentation of this stimulus. The unconditioned face however did require cortical processing to generate an adequate response, hence selective attention was increased. Assuming that the brain strives for the highest level of efficiency in processing visual information, presentation of a conditioned angry face therefore did not lead to 'unnecessary' cortical processing.

It is also possible to explain the enhanced P1 amplitudes to unconditioned faces in terms of defensive behaviour to *potential* danger and the reduced P1 amplitudes to conditioned faces terms as defensive behaviour to *effective* danger. Evolutional survival of all species depends on an array of behavioural response patterns that are available to cope with potential or actual threats, such as predators. The amygdala has a crucial role in initiating defensive behaviour to known objects, places or animals that present imminent danger, but also in activating neural systems which increase arousal, vigilance and selective attention to input that represents potential danger (cf. Misslin, 2003). The conditioned angry faces may have acted as 'clear and present danger', since its presentation is highly predictive of the unpleasant

experience of the loud white noise burst that was previously paired with this stimulus during the conditioning phase. The reduced P1 therefore is an adequate fear response to this threat as reduced selective attention is consistent with freeze, flight or avoidance behaviour. The unconditioned angry face on the other hand, was never paired with the white noise but still represents a potential threat because an angry emotional facial expression in general is a good predictor of looming unpleasantness and also bears some resemblance to the conditioned angry face. To determine the most adequate response to this potential threat (e.g. fight, flight, avoidance or approach), further exploration is required; hence selective attention was enhanced, resulting in a higher P1 amplitude.

9.2 Dissociations between overt and covert visual processing

Overt, or explicit, visual processing refers to the conscious perception of visual information. Covert, or implicit, visual processing, on the other hand refers to unconscious perception of visual information. Covert visual processing can be revealed when conscious processing of a distinct type of visual information is precluded, for instance due to a perceptual disorder, while performance on tasks measuring this type of visual processing indicates that a certain level of visual perception still occurs. Dissociations between overt and covert processing are not limited to visual processing as they can also be found in other domains, such as memory, language and attention (see Weiskrantz (1997), for an overview).

In patients with visual perceptual disorders, assessment of covert perception has been used to demonstrate preserved processing. Covert processing can also be assessed in healthy subjects, for instance when backward masking prevents conscious perception of visual information. The different techniques that are available to evaluate covert processing can be divided into physiological indexes and behavioural indexes (Bruyer, 1991; Schweinberger & Burton, 2003). The physiological measures that were used in the experimental studies described in this thesis are Skin Conductance Response (SCR) and ERPs. The decision times in the face recognition task described in the experimental study with JS (*chapter 5*) may be interpreted as a behavioural measure of covert processing.

The question has been raised whether covert visual processing is qualitatively different or just quantitatively different from overt processing (Weiskrantz, 2004), and, to complicate things even further, it has also been suggested that different measures of covert visual processing may in fact reflect different underlying mechanisms (Schweinberger & Burton, 2003). In the following section, the differences between covert and overt processing, observed in the experimental studies, will be discussed in the light of these questions.

Patient JS, described in *chapter 5*, has impaired overt recognition of faces – especially faces of close family members. The data from the experimental recognition task provided two indications that covert processing of faces was still intact. The most apparent evidence was provided by the increased SCRs to family members. Second, one could argue that the increased decision times to photographs of family members may also reflect covert processing. If covert recognition would have been completely absent, then the decision time to incorrect responses to photographs of family members would be comparable to decision times of correct responses to unfamiliar faces. The decision to press "no" to family members, however, took much more time than pressing "no" to unfamiliar faces. In fact, there was no significant difference between decision times of correct and incorrect responses. The longer decision times to family members compared to unfamiliar faces therefore indicate that some form of covert recognition is still intact.

Three types of explanation for covert face recognition have been put forward. The first interprets the dissociations between overt and covert recognition as evidence for separate visual processing streams (e.g. Bauer, 1984; Ellis & Young, 1990 and Gobbini & Haxby, 2007). The second interprets these dissociations in terms of a disconnection between intact 'early' visual processing and later processes related to conscious awareness (e.g. De Haan et al., 1992; Tranel & Damasio, 1988). The third relates covert processing to degraded representational quality, which would make it impossible for impoverished representations to become conscious (e.g. Farah et al., 1993).

It would be hard to explain the discrepancy between covert and overt recognition of faces found in JS in terms of a diminished network for face recognition. Since JS is more impaired at (overtly) recognizing family members than at recognizing other people, this explanation would imply that the neural networks underlying recognition of family members would somehow be more impoverished

than the networks underlying recognition of other people. The same holds for an explanation in terms of a disconnection between lower and higher processes, as this would require that the network underlying family recognition would be selectively 'more disconnected' than the network underlying recognition of other people. In case of JS, the explanation that covert and overt recognition are produced by different visual processing streams, for instance ventral for face recognition and subcortical for emotional relevance, may be more suitable, since overt recognition was more impaired for emotionally significant people than for emotionally neutral people. However, it should be noted that none of these explanations can be ruled out on the basis of the current data, as only two measures of covert processing were used in this experiment. Also, it could be possible that different types of covert face processing exist, and that different measures reflect discrete types of covert processing.

In the same chapter, it was also addressed whether the SCRs measured in JS reflected the same type of covert processing as was observed in the control subjects. One possibility that was put forward is that the SCRs in JS might have been produced by the affective face processing route as proposed by Ellis and Young (1990). However, as JS' SCR amplitudes and SCR latencies showed a different pattern compared to controls, it was also proposed that her SCRs might be an indication of the emotional arousal that is generated by a delusional attribution process rather than a direct manifestation of covert recognition. This delusional attribution process might also have been the cause of her prolonged decision times to close family members. Schweinberger and Burton (2003) proposed that the different behavioural indexes of covert face processing are mediated by the same mechanisms as overt recognition, while SCRs might be mediated by a different mechanism. It is difficult to maintain this argument for the prolonged decision times observed in JS. First, prolonged decision times were only observed in response to family members and not to celebrities, while recognition of the latter category was also impaired (albeit less impaired than recognition of family members). This indicates that the decision times reflect a different mechanism than the one for overt recognition. Second, the results suggest that the prolonged decision times and the enhanced SCRs might reflect the same underlying mechanism, although it could be questioned whether this mechanism is primarily related to face recognition or to the delusional aspects of the impaired face processing observed in JS.

As was proposed in the previous paragraph, both ERP experiments presented in this thesis (*chapters 6 and 7*) indicate that ERPs to masked faces and unmasked faces reflect processing via different visual processing routes. It was argued that ERPs to masked stimuli reflected subcortical visual processing (i.e. a modulation of the visual cortex by subcortical structures), while ERPs to unmasked stimuli reflected cortical visual processing – most likely via the ventral stream, which is highly specialized for processing face-related information. As was pointed out in *chapter 2*, visual processing is quasi-hierarchical since multiple reciprocal connections exist between successive processing stages of cortical processing (Van Essen et al., 1992). Hence, communication between different stages of cortical processing is not unidirectional. When presentation of the faces was masked, perceptual consolidation of the face via re-entrant projections was interrupted by processing of the mask (Di Lollo et al., 2000; Enns & Di Lollo, 2000). Since the masked faces only reached the initial stages of visual processing, conscious perception via later stages was precluded. Hence, EPRs to masked stimuli primarily reflected a modulation of the visual cortex by subcortical structures and not cortical processing.

But does this also imply that the opposite is true for unmasked stimuli? Are subcortical structures not at all involved in processing of the mask? It could be argued that subcortical projections to the visual cortex did also occur in response to the mask, but at a later point in time. Remember that when the masks were manipulated, they were always preceded by brief presentation of a neutral face. It could be the case that modulation of the cortex in response to the target is reflected by P1, while modulation in response to the mask is reflected by the N170. Indeed, the interval between P1 and N170 has about the same length as the interval between the onset of the target and the onset of the mask. However, this explanation should be dismissed because the effect of aversive conditioning was that was found in P1 to masked stimuli was not found in N170 to unmasked stimuli. Also, in the experiment with FZ, a double dissociation was found between the effects of subliminal and supraliminal presentation on the P170 component. In these experimental studies, processing of the target therefore was qualitatively different from processing of the mask.

As obvious and attractive as this interpretation may seem, it also causes a major problem. Since the masked stimuli were presented for only 17 ms, it may be inferred that thalamo-amygdalar processing is both extremely quick and extremely sensitive. Also, the modulation of the visual cortex via afferent projections to this

region occurred within a time-frame of 100 ms, since the P1 starts its curve around 100 ms post stimulus-onset. Why were the effects of these subcortical projections only observed when the target preceding the mask was manipulated and not when the mask itself was manipulated? It could be the case that subcortical structures only responded to the first stimulus that was presented, namely the target, and not to the second stimulus that was presented briefly afterwards. In other words, thalamo-amygdalar processing might have suffered from 'forward masking' when the critical manipulation occurred in the mask, while cortical processing might have suffered from 'backward masking' when the critical manipulation occurred in the target. This may also explain the current discrepancy between studies using backward masking paradigms to assess emotional processing and studies using only supraliminal presentation of emotional stimuli. Most neuro-imaging studies employing a masking paradigm reported enhanced amygdala activity to masked emotional stimuli compared to unmasked emotional stimuli, both in healthy subjects (Morris et al., 1999; Williams et al., 2006) and in patients with depression (Sheline et al., 2001) or post-traumatic stress disorder (PTSD) (Armony et al., 2005; Rauch et al., 2000). When normal presentation of stimuli (i.e. no masking paradigm) was used however, imaging studies showed increased amygdala activity to conscious presentation of emotional stimuli (Keightley et al., 2003; Morris et al., 1996; Stein et al., 2002; Yoon et al., 2007).

The same discrepancy can be seen in ERP studies: in those studies employing masking, effects on early EPR components were found to masked images of facial emotional expressions (Williams et al., 2004), but not when these stimuli were preceded by neutral stimuli (Rossignol et al., 2005). ERP studies that used normal presentation of emotional stimuli without masking, showed effects of emotional processing on early ERP components (Batty & Taylor, 2003; Sato et al., 2001; Schupp et al., 2007; Smith et al., 2003). It may thus be concluded that in visual masking, covert processing of emotional stimuli is qualitatively different from overt processing, while at the same time it should be noted that subcortical brain structures are not exclusively linked to covert processing. As Enns and Di Lollo (2000) stated: when using masking as a tool for probing underlying perceptual mechanisms, "…it is important to note that the mechanisms under investigation are not inherently tied to backward masking; masking simply makes them more readily apparent."

9.3 Impaired visual processing

When damage occurs to a part of the brain that is directly or indirectly involved in processing visual information, visual processing may become impaired. Since different parallel yet interacting processing streams underlie visual processing, the consequences of damage to the visual system depend strongly on the level at which the damage takes place. In *chapter 2*, it was illustrated how visual processing may be impaired as a result of damage to different brain structures. In the following section, some of the visual impairments that were described in this thesis will be discussed.

In some cases, impaired visual processing is caused by the destruction of brain structures in which specific representations of visual information are located. The most compelling example of this type of damage is homonymous hemianopia. Impaired visual processing may also be the result of an interruption of the transmission of visual processing occurring at some point within a visual processing stream. For instance, different forms of associative agnosia may be exemplary of this type of damage. As the different visual processing streams are extensively interconnected, damage occurring to a brain region primarily associated with one stream may also affect processing of the other streams. Moreover, impaired visual processing may also be the result of a disrupted connection or interaction between two processing streams.

In *chapter 7*, it was demonstrated that destruction of the right amygdala caused impaired overt recognition of fear. The ERP data showed that at least some level of cortical processing of fear was still intact, but this clearly was not enough to allow overt recognition of fear. The results also showed that right amygdala damage did not affect classical conditioning. These results thus indicate that the right amygdala is necessary for recognition of fearful facial expression, but not for aversive conditioning. Conversely, the left amygdala on its own appears to be capable of associative learning but not of recognition of fearful facial expression.

Although only healthy subjects without brain damage participated in the ERP experiment described in *chapter 6*, some subjects showed less specific amygdala function than others. This effectiveness of the modulatory role of the amygdala was related to trait-anxiety, as measured by a questionnaire. Subjects with high trait-anxiety, indicative of neuroticism, had higher P1 amplitudes to all stimuli compared to subjects with low trait-anxiety. Crucially, while subjects with low-trait anxiety

showed reduced P1 amplitudes to the aversively conditioned angry face, in subjects with high trait-anxiety P1 amplitudes to the conditioned face were not reduced. In the previous sections, differences in P1 amplitudes were interpreted in terms of enhanced or reduced cortical selective attention via afferent projections of the amygdala. According to one interpretation, *effective* danger prompted reduced selective attention, compatible with fright, flight and avoidance behaviour, while *potential* danger prompted enhanced selective attention, compatible with increased vigilance and explorative behaviour. Along these lines, the data presented in this study suggest that people with high trait-anxiety have more attentive processing of fear-inducing stimuli, and also have a less effective automatic modulation of attentional processing of fear-inducing stimuli. Increased amygdala activity in response to emotional stimuli has been found in subjects with high trait-anxiety (Etkin et al., 2004), and in patients with PTSD (Armony et al., 2005; Rauch et al., 2000), or social phobia (Birbaumer et al., 1998; Stein et al., 2002; Yoon et al., 2007). The results presented in this thesis indicate that in subjects with high, yet non-pathological, trait-anxiety, the amygdala is more prone to make an overgeneralization of responses to fearful stimuli than in subjects with low trait-anxiety. Whether this overgeneralization by the amygdala is the cause of the higher level of experienced fear in daily life or vice versa cannot be inferred from this ERP study or from the aforementioned neuro-imaging studies, and needs to be addressed in future research.

As mentioned at the start of this section, visual impairments may also occur as a result of a disrupted connection or interaction between two processing streams. Although to some extent, this may appear to be a more hypothetical cause of impaired visual processing; this possibility was proposed in *chapter 5*. Patient JS suffered from face recognition problems after ischaemic stroke. Unlike prosopagnosia, recognition of familiar faces was more impaired for emotionally significant people. Also, in some cases, impaired recognition was accompanied by a delusional belief. For instance, JS believed her grandchildren looked ugly. One of the explanations for this phenomenon was that JS' impairment was caused by a failing interaction between a system for overt face recognition and a covert, affect-related, face-processing system. Whether a failing interaction between visual streams is indeed the most suitable explanation for the impairments observed in JS or not, the notion that brain damage that occurs in one of the processing streams not only impairs the type of visual processing that is

primarily related to that stream, but may also alter the way that stream interacts with other streams may still be important.

9.4 Rehabilitation of function after damage to the visual streams

In *chapters 3 and 4*, rehabilitation methods for homonymous visual field defects and unilateral neglect were reviewed. When evaluating and comparing therapeutic interventions or rehabilitation therapies aiming to improve functioning for individuals with brain damage, it is important to (1) understand that different approaches to recovery exist, (2) determine which approach is used in a specific intervention, and (3) decide which type of evidence is required to ascertain the effectiveness of the therapeutic intervention.

According to a model proposed by Code, two mechanisms underlie recovery: restoration and compensation. Both mechanisms may operate on different levels, namely neural, cognitive and behavioural (Code, 2001). Robertson and Murre stressed that the type of recovery that may occur at the neural level first of all depends on the degree of lesioning caused by brain damage (Robertson & Murre, 1999). In minor or *mild* lesions, autonomous recovery may occur within a damaged system. Obviously, rehabilitation is not necessary in these cases. With *moderate* lesioning, neural representations are potentially re-usable and restitution of function may be possible with guided recovery. Robertson and Murre (1999) proposed that there are five different approaches for guided recovery after brain damage: non-specific stimulation, bottom-up specific stimulation, top-down specific stimulation, inhibitory processes and manipulation of arousal mechanisms. When lesions are *severe*, only compensation by other brain areas is possible. Compensatory processes would be implicated when the neuropsychological processes generating the pattern of behaviour in a given domain is unambiguously different from the processes in non-brain-damaged people. Restitution on the other hand, can not be proven by behavioural methods, but requires physical measures of brain structure and function, clearly demonstrating that neuroanatomical structures which are known to be involved in the impaired function are activated when the relevant behaviour is produced (Robertson & Murre, 1999).

It is evident that the two therapies that were evaluated in *chapter 3*, namely scanning compensatory therapy (SCT) and vision restoration therapy (VRT) represent very different approaches. In terms of the model proposed by Code (2001), SCT involves a compensatory mechanism, operating at least on a behavioural level and possibly to a certain extent on a cognitive level. According to Robertson and Murre (1999), this implies that SCT is applicable in patients with lesions ranging from mild to severe. Also, it means that behavioural methods are adequate to confirm the effectiveness of the intervention. VRT on the other hand, involves an approach aiming at restoration on a neural level, as VRT is based on the assumption that it activates surviving neurons in areas of residual vision – that is, areas that are partially damaged (Kasten et al., 1998; Kasten et al., 1999; Kasten et al., 2000; Sabel et al., 1997). In terms of Robertson and Murre's model, VRT is constituted of guided recovery via bottom-up specific stimulation (Robertson & Murre, 1999). Hence, behavioural methods do not suffice to prove that restitution actually takes place, but methods verifying that function is regained within the occipital cortex are also required.

As was mentioned in the systematic review (*chapter 3*), considerable disagreement exists as to which method of perimetry should be used to establish the alleged expansion of the visual field (Balliet et al., 1985; Reinhard et al., 2005), and it is important that this matter should be resolved to measure therapy outcome objectively (Bouwmeester et al., 2007). The current debate on this subject focuses primarily on the question which methods of perimetry are reliably and valid enough to measure the visual field and, for instance, exclude the possibility of eye movements or para-central fixation. Following Robertson and Murre's line of reasoning however, the real proof of the pudding would be provided by functional imaging data showing an increase in activity in the damaged visual cortex after training.

Most of the therapeutic interventions aiming to reduce neglect symptoms that were described in *chapter 4* aim at guided recovery of impaired neural networks via bottom-up specific stimulation, reduction of inhibitory competition, manipulation of arousal mechanisms or joint activation of mutually facilitatory networks. As interesting and appealing as these methods may seem from a theoretical perspective, a recent systematic review indicated that visual scanning training, which may be regarded as a compensation strategy acting on a behavioural level, is at least as effective as these methods (Luaute et al., 2006). However, this should not mean that research should not focus on finding ways to recover visual function at a neuronal

level via guided recovery. Some of these methods are indeed very promising and provide further insight in the way visual processing streams interact. However, for patients with visual perceptual impairments, like all patients suffering from brain damage, the most important goal of rehabilitation is to achieve a higher level of participation in various social areas such as family, work and leisure. This also appears to be the case for JS and FZ. In spite of the attractiveness of the suggestion that rehabilitation should focus on 'discovering' preserved covert visual processing (Bruyer, 1991), these patients learned behavioural strategies that helped them to overcome some of the consequences of their perceptual deficits. JS for instance, has learned to rely on recognition of voices instead of faces, and when family members pay her a visit, they make a phone call only moments before they ring at her door.

In this context, a study by Adolphs and Tranel is of particular interest (Adolphs & Tranel, 2003). They assessed recognition of emotional scenes in patients with bilateral amygdala lesions, patients with unilateral amygdala lesions, patients with brain damage not involving the amygdala, and healthy controls. As expected, bilateral amygdala patients performed worse in labelling emotional scenes in which the facial expressions of the people depicted were visible. However, when faces were erased in scenes depicting anger, their performance was superior to that of all control groups. This effect thus provides a different perspective on rehabilitation methods for specific perceptual disorders after damage to the visual system: instead of training to improve recognition of facial emotional expressions in amygdala patients or to improve face recognition in patients with prosopagnosia, training might result in becoming experts at recognizing body language or inferring someone's identity via clothes or other specific details.

9.4 Concluding remarks

This thesis focused on the different processing streams that underlie visual perception and on the interactions between these streams. Damage to brain structures that are directly or indirectly involved in visual processing may lead to specific impairments of visual perception. Several impairments were described in this thesis, either when evaluating rehabilitation methods, or in the light of a distinction between covert and overt visual processing.

Some of the interactions between the visual processing streams were discussed, in particular those involved in recognition of faces and facial emotional expressions. In most cases, we are not consciously aware of the ongoing process of emotional evaluation of visual input, and its function may not be assessed directly. In this thesis, visual masking was used to assess the interaction between the subcortical and cortical visual processing streams. It was argued that brain structures implicated in subcortical visual processing, especially the amygdala, may modulate the visual cortex pre-attentively, to facilitate awareness of emotionally relevant information that requires enhanced processing. Conversely, subcortical brain structures may reduce attention to information that does not require enhanced processing. In people who experience relatively much fear in everyday life, this modulatory role of subcortical structures may be less efficient. Also, when damage occurs to the amygdala, processing of specific facial emotional expressions may become impaired. Emotion-related visual processing may also play a role in the recognition of close family members.

Knowledge of the visual system and the interactions between visual processing streams has accumulated significantly over the past few decades, and served to develop numerous treatments for visual perceptual impairments. In some cases, specific interventions may help to restore function and to overcome these impairments. In many cases however, learning compensatory strategies may still be the most adequate method to improve functioning in daily life. Further research of the mechanisms underlying overt end covert visual processing may contribute to a better understanding of the interactions between visual processing streams and may also help to develop new rehabilitation methods.

References

Adolphs, R. & Tranel, D. (2003). Amygdala damage impairs emotion recognition from scenes only when they contain facial expressions. *Neuropsychologia, 41,* 1281-1289.

Adolphs, R. & Tranel, D. (2004). Impaired judgments of sadness but not happiness following bilateral amygdala damage. *Journal of Cognitive Neuroscience, 16,* 453-462.

Adolphs, R., Tranel, D., Hamann, S., Young, A. W., Calder, A. J., Phelps, E. A. et al. (1999). Recognition of facial emotion in nine individuals with bilateral amygdala damage. *Neuropsychologia, 37,* 1111-1117.

Armony, J. L., Corbo, V., Clement, M. H., & Brunet, A. (2005). Amygdala response in patients with acute PTSD to masked and unmasked emotional facial expressions. *American Journal of Psychiatry, 162,* 1961-1963.

Balliet, R., Blood, K. M., & Rita, P. (1985). Visual field rehabilitation in the cortically blind? *Journal of Neurology, Neurosurgery and Psychiatry, 48,* 1113-1124.

Batty, M. & Taylor, M. J. (2003). Early processing of the six basic facial emotional expressions. *Cognitive Brain Research, 17,* 613-620.

Bauer, R. M. (1984). Autonomic recognition of names and faces in prosopagnosia: a neuropsychological application of the Guilty Knowledge Test. *Neuropsychologia, 22,* 457-469.

Birbaumer, N., Grodd, W., Diedrich, O., Klose, U., Erb, M., Lotze, M. et al. (1998). fMRI reveals amygdala activation to human faces in social phobics. *Neuroreport, 9,* 1223-1226.

Bouwmeester, L., Heutink, J., & Lucas, C. (2007). The effect of visual training for patients with visual field defects due to brain damage: a systematic review. *Journal of Neurology, Neurosurgery and Psychiatry, 78,* 555-564.

Bruce, V. & Young, A. (1986). Understanding face recognition. *British Journal of Psychology, 77 (Pt 3),* 305-327.

Bruyer, R. (1991). Covert face recognition in prosopagnosia: a review. *Brain Cogn, 15,* 223-235.

Calder, A. J., Young, A. W., Rowland, D., Perrett, D. I., Hodges, J. R., & Etcoff, N. L. (1996). Facial emotion recognition after bilateral amygdala damage: differentially severe impairment of fear. *Cognitive Neuropsychology, 13,* 699-745.

Code, C. (2001). Multifactorial processes in recovery from aphasia: developing the foundations for a multileveled framework. *Brain and Language, 77,* 25-44.

De Haan, E. H. F., Bauer, R. M., & Greve, K. W. (1992). Behavioural and physiological evidence for covert face recognition in a prosopagnosic patient. *Cortex, 28,* 77-95.

Di Lollo, V., Enns, J. T., & Rensink, R. A. (2000). Competition for consciousness among visual events: the psychophysics of reentrant visual processes. *Journal of Experimental Psychology: General, 129,* 481-507.

Doron, N. N. & LeDoux, J. E. (1999). Organization of projections to the lateral amygdala from auditory and visual areas of the thalamus in the rat. *Journal of Computational Neurology, 412,* 383-409.

Eimer, M. (2000a). Event-related brain potentials distinguish processing stages involved in face perception and recognition. *Clinical Neurophysiology, 111,* 694-705.

Eimer, M. (2000b). The face-specific N170 component reflects late stages in the structural encoding of faces. *Neuroreport, 11,* 2319-2324.

Eimer, M. & Holmes, A. (2002). An ERP study on the time course of emotional face processing. *Neuroreport, 13,* 427-431.

Ellis, H. D. & Young, A. W. (1990). Accounting for delusional misidentifications. *British Journal of Psychiatry, 157,* 239-248.

Enns, J. T. & Di Lollo, V. (2000). What's new in visual masking? *Trends in Cognitive Sciences, 4,* 345-352.

Etkin, A., Klemenhagen, K. C., Dudman, J. T., Rogan, M. T., Hen, R., Kandel, E. R. et al. (2004). Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. *Neuron, 44,* 1043-1055.

Farah, M. J., Oreilly, R. C., & Vecera, S. P. (1993). Dissociated Overt and Covert Recognition As An Emergent Property of A Lesioned Neural-Network. *Psychological Review, 100,* 571-588.

Foxe, J. J. & Simpson, G. V. (2002). Flow of activation from V1 to frontal cortex in humans. A framework for defining "early" visual processing. *Experimental Brain Research, 142,* 139-150.

Gobbini, M. I. & Haxby, J. V. (2007). Neural systems for recognition of familiar faces. *Neuropsychologia, 45,* 32-41.

Heinze, H. J., Mangun, G. R., Burchert, W., Hinrichs, H., Scholz, M., Munte, T. F. et al. (1994). Combined spatial and temporal imaging of brain activity during visual selective attention in humans. *Nature, 372,* 543-546.

Holmes, A., Vuilleumier, P., & Eimer, M. (2003). The processing of emotional facial expression is gated by spatial attention: evidence from event-related brain potentials. *Cognitive Brain Research, 16,* 174-184.

Kasten, E., Poggel, D. A., Muller-Oehring, E., Gothe, J., Schulte, T., & Sabel, B. A. (1999). Restoration of vision II: residual functions and training-induced visual field enlargement in brain-damaged patients. *Restorative Neurology and Neuroscience, 15,* 273-287.

Kasten, E., Poggel, D. A., & Sabel, B. A. (2000). Computer-based training of stimulus detection improves color and simple pattern recognition in the defective field of hemianopic subjects. *Journal of Cognitive Neuroscience, 12,* 1001-1012.

Kasten, E., Wuest, S., & Sabel, B. A. (1998). Residual vision in transition zones in patients with cerebral blindness. *Journal of Clinical and Experimental Neuropsychology, 20,* 581-598.

Keightley, M. L., Winocur, G., Graham, S. J., Mayberg, H. S., Hevenor, S. J., & Grady, C. L. (2003). An fMRI study investigating cognitive modulation of brain regions associated with emotional processing of visual stimuli. *Neuropsychologia, 41,* 585-596.

LeDoux, J. E. (1996). *The Emotional Brain*. New York: Touchstone.

LeDoux, J. E. (2002). *Synaptic Self*. New York: Viking.

LeDoux, J. E., Sakaguchi, A., & Reis, D. J. (1984). Subcortical efferent projections of the medial geniculate nucleus mediate emotional responses conditioned to acoustic stimuli. *Journal of Neuroscience, 4,* 683-698.

Luaute, J., Halligan, P., Rode, G., Rossetti, Y., & Boisson, D. (2006). Visuo-spatial neglect: a systematic review of current interventions and their effectiveness. *Neuroscience and Biobehavioral Reviews, 30,* 961-982.

McDonald, J. J., Ward, L. M., & Kiehl, K. A. (1999). An event-related brain potential study of inhibition of return. *Perception and Psychophysics, 61,* 1411-1423.

Misslin, R. (2003). The defense system of fear: behavior and neurocircuitry. *Neurophysiologie Clinique, 33,* 55-66.

Morris, J. S., Frith, C. D., Perrett, D. I., Rowland, D., Young, A. W., Calder, A. J. et al. (1996). A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature, 383,* 812-815.

Morris, J. S., Öhman, A., & Dolan, R. J. (1998). Conscious and unconscious emotional learning in the human amygdala. *Nature, 393,* 467-470.

Morris, J. S., Öhman, A., & Dolan, R. J. (1999). A subcortical pathway to the right amygdala mediating "unseen" fear. *Proceedings of the National Academy of Sciences of the United States of America, 96,* 1680-1685.

Pizzagalli, D., Regard, M., & Lehmann, D. (1999). Rapid emotional face processing in the human right and left brain hemispheres: an ERP study. *Neuroreport, 10,* 2691-2698.

Rauch, S. L., Whalen, P. J., Shin, L. M., McInerney, S. C., Macklin, M. L., Lasko, N. B. et al. (2000). Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. *Biological Psychiatry, 47,* 769-776.

Reinhard, J., Schreiber, A., Schiefer, U., Kasten, E., Sabel, B. A., Kenkel, S. et al. (2005). Does visual restitution training change absolute homonymous visual field defects? A fundus controlled study. *British Journal of Ophthalmology., 89,* 30-35.

Robertson, I. H. & Murre, J. M. (1999). Rehabilitation of brain damage: brain plasticity and principles of guided recovery. *Psychological Bulletin, 125,* 544-575.

Rossignol, M., Philippot, P., Douilliez, C., Crommelinck, M., & Campanella, S. (2005). The perception of fearful and happy facial expression is modulated by anxiety: an event-related potential study. *Neuroscience Letters, 377,* 115-120.

Sabel, B. A., Kasten, E., & Kreutz, M. R. (1997). Recovery of vision after partial visual system injury as a model of postlesion neuroplasticity. *Advances in Neurology, 73,* 251-276.

Sato, W., Kochiyama, T., Yoshikawa, S., & Matsumara, M. (2001). Emotional expression boosts ealy visual processing of the face: ERP recording and its decomposition by independent component analysis. *Neuroreport, 12,* 709-714.

Schupp, H. T., Cuthbert, B. N., Bradley, M. M., Cacioppo, J. T., Ito, T., & Lang, P. J. (2000). Affective picture processing: the late positive potential is modulated by motivational relevance. *Psychophysiology, 37,* 257-261.

Schupp, H. T., Stockburger, J., Codispoti, M., Junghofer, M., Weike, A. I., & Hamm, A. O. (2007). Selective visual attention to emotion. *Journal of Neuroscience, 27,* 1082-1089.

Schweinberger, S. R. & Burton, A. M. (2003). Covert recognition and the neural system for face processing. *Cortex, 39,* 9-30.

Scott, S. K., Young, A. W., Calder, A. W., Hellawell, D. J., Aggleton, J. P., & Johnson, M. (1997). Impaired auditory recognition of fear and anger following bilateral amygdala lesions. *Nature, 385,* 254-257.

Sheline, Y. I., Barcg, D. M., Donnely, J. M., Ollinger, J. M., Snyder, A. Z., & Mintun, M. A. (2001). Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biological Psychiatry, 50,* 651-658.

Smith, N. K., Cacioppo, J. T., Larsen, J. T., & Chartrand, T. L. (2003). May I have your attention, please: electrocortical responses to positive and negative stimuli. *Neuropsychologia, 41,* 171-183.

Stein, M. B., Goldin, P. R., Sareen, J., Zorrilla, L. T. E., & Brown, G. G. (2002). Increased amygdala activation to angry and contemptuous faces in generalized social phobia. *Archives of General Psychiatry, 59,* 1027-1034.

Streit, M., Ioannides, A. A., Liu, L., Wolwer, W., Dammers, J., Gross, J. et al. (1999). Neurophysiological correlates of the recognition of facial expressions of emotion as revealed by magnetoencephalography. *Cognitive Brain Research, 7,* 481-491.

Streit, M., Wolwer, W., Brinkmeyer, J., Ihl, R., & Gaebel, W. (2000). Electrophysiological correlates of emotional and structural face processing in humans. *Neuroscience Letters, 278,* 13-16.

Tranel, D. & Damasio, A. R. (1988). Non-conscious face recognition in patients with face agnosia. *Behavioural Brain Research, 30,* 235-249.

Van Essen, D. C., Anderson, C. H., & Felleman, D. J. (1992). Information-Processing in the Primate Visual-System - An Integrated Systems Perspective. *Science, 255,* 419-423.

Weiskrantz, L. (1997). *Consiousness lost and found. A neuropsychological explanation*. Oxford: Oxford University Press.

Weiskrantz, L. (2004). Blindsight. In L.M.Chalupa & J. S. Werner (Eds.), *The Visual Neurosciences* (pp. 657-669). Cambridge (MA): MIT Press.

Whalen, P. J., Rauch, S. L., Etcoff, N. L., McInerney, S. C., Lee, M. B., & Jenike, M. A. (1998). Masked presentations of emotional facial expressions modulate amygdala activity without explicit knowledge. *Journal of Neuroscience, 18,* 411-418.

Williams, L. M., Liddell, B. J., Kemp, A. H., Bryant, R. A., Meares, R. A., Peduto, A. S. et al. (2006). Amygdala-prefrontal dissociation of subliminal and supraliminal fear. *Human Brain Mapping, 27,* 652-661.

Williams, L. M., Liddell, B. J., Rathjen, J., Brown, K. J., Gray, J., Phillips, M. et al. (2004). Mapping the time course of nonconscious and conscious perception of fear: an integration of central and peripheral measures. *Human Brain Mapping, 21,* 64-74.

Yoon, K. L., Fitzgerald, D. A., Angstadt, M., McCarron, R. A., & Phan, K. L. (2007). Amygdala reactivity to emotional faces at high and low intensity in generalized social phobia: a 4-Tesla functional MRI study. *Psychiatry Research, 154,* 93-98.

Zald, D. H. (2003). The human amygdala and the emotional evaluation of sensory stimuli. *Brain Research Reviews, 41,* 88-123.

Samenvatting

Samenvatting

Voor de meeste mensen is zien een van de meest vanzelfsprekende zaken die er bestaan. Om goed te kunnen zien hebben we behalve goede ogen en voldoende licht ook een gezond brein nodig. Ons brein geeft betekenis aan de informatie die via onze ogen binnenkomt. Omdat het zien het dominante zintuig is voor mensen, is een groot deel van ons brein direct of indirect betrokken bij het verwerken van visuele informatie. Het brein is bovendien dusdanig georganiseerd dat verschillende typen visuele informatie door afzonderlijke delen van de hersenen worden verwerkt.

Dit proefschrift beschrijft de verschillende 'routes' die visuele informatie in de hersenen kan afleggen en de wijze waarop deze routes met elkaar interacteren. Beschadiging van bepaalde delen van het brein die, direct of indirect, betrokken zijn bij de verwerking van visuele informatie kan leiden tot specifieke stoornissen in het zien. Een aantal van deze stoornissen wordt in dit proefschrift besproken en van een tweetal veel voorkomende visuele stoornissen na een hersenbeschadiging worden de mogelijkheden voor revalidatie besproken.

In *hoofdstuk 2* wordt beschreven welke hersenstructuren betrokken zijn bij de verwerking van visuele informatie. Vervolgens worden drie routes voor visuele informatieverwerking beschreven.

In het netvlies (retina) van het oog wordt licht omgezet in elektrische signalen. Deze signalen worden via zogenoemde ganglioncellen naar het brein geprojecteerd. Er bestaan meerdere typen ganglioncellen, waarvan de uitlopers (axonen) samen de oogzenuw (nervus opticus) vormen. De oogzenuwen van de beide ogen kruisen elkaar in het optisch chiasma zodanig dat informatie uit het linkergezichtsveld door de rechterhersenhelft wordt verwerkt en informatie vanuit het rechtergezichtsveld door de linkerhersenhelft wordt verwerkt. Zowel het linker- als het rechteroog stuurt dus informatie naar de beide hersenhelften. Na het optisch chiasma wordt visuele informatie voorbewerkt door de laterale genuculate kernen (nuclei) van de thalamus. Vanuit dit deel van de thalamus wordt de informatie doorgestuurd naar de visuele cortex en naar delen van het 'oudere' limbische systeem. In de visuele cortex wordt de informatie stap voor stap verwerkt door hersengebieden met een toenemende mate van specialisatie voor een bepaald soort informatie. De meest primaire verwerkingsstadia vinden plaats in de hersengebieden die zich achterin het brein

bevinden, de occipitale cortex, terwijl de latere verwerkingsstadia door meer anterieur gelegen hersengebieden wordt verzorgd. In deze latere stadia van visuele informatieverwerking kan een onderscheid worden gemaakt tussen twee hoofdwegen: de 'wat' en de 'waar' route. De 'wat' route, ook wel de ventrale route genoemd, is vooral betrokken bij het herkennen van voorwerpen en gezichten. De 'waar' route, ook wel de dorsale route genoemd, is vooral betrokken bij het waarnemen van ruimte en beweging, het bepalen van de plaats van objecten en het integreren van deze informatie met het motorische systeem, zodat we bijvoorbeeld in staat zijn om met een eenvoudige beweging objecten op te pakken. Behalve via deze twee corticale routes, wordt visuele informatie ook verwerkt door dieper gelegen, subcorticale hersengebieden. Informatie vanuit de thalamus wordt namelijk niet alleen naar de visuele cortex geprojecteerd, maar ook naar de amygdalakernen. Deze amygdalakernen zijn vooral betrokken bij de verwerking van emotioneel relevante informatie, zoals gezichtsuitdrukkingen.

De routes voor visuele informatieverwerking zijn onderling met elkaar verbonden, zodat ze kunnen interacteren en elkaar kunnen moduleren. Een voorbeeld van een dergelijke interactie tussen twee routes wordt geschetst in het model van LeDoux. Volgens LeDoux kan een emotionele stimulus op twee manieren worden verwerkt, namelijk via de 'high road' of via de 'low road'. Via de 'high road' wordt informatie door de thalamus doorgestuurd naar de visuele cortex, waar de informatie in meerdere stappen verder wordt verwerkt. Vervolgens wordt de informatie vanuit de cortex geprojecteerd naar de amygdala, die een emotionele reactie genereert. Wanneer emotionele informatie wordt verwerkt via de 'low road', wordt de corticale verwerking feitelijk overgeslagen en projecteert de thalamus rechtstreeks naar de amygdala. Beide routes zouden elk hun voor- en nadelen hebben. Een voordeel van de 'high road' is dat door de hoge mate van specialisatie een nauwkeurige analyse wordt gemaakt van de emotionele stimulus, alvorens via de amygdala een respons wordt gegenereerd. Een nadeel is echter dat deze nauwkeurige analyse tijd kost. Deze tijd kan in een potentieel bedreigende situatie juist nodig zijn om een snelle reactie op de stimulus uit te voeren. Het voordeel van de 'low road' is dat hierdoor wel een snelle reactie kan worden gegeven op directe dreiging van gevaar. Omdat de nauwkeurige analyse via de cortex echter wordt overgeslagen, is de 'low road' minder accuraat. Hierdoor kan het bijvoorbeeld voorkomen dat een snelle schrikreactie volgt op een visuele stimulus die globaal de kenmerken heeft van iets bedreigends, maar dat in

werkelijkheid niet is, zoals een rubberen namaakspin. Een gevolg van de verbindingen tussen de subcorticale en corticale verwerkingsroutes is dat emotioneel relevante informatie als het ware een voorkeursbehandeling krijgt in de verdere verwerking ten opzichte van minder relevante informatie.

In dit proefschrift worden diverse gevolgen van beschadigingen van het visuele systeem beschreven. Een van deze gevolgen is homonieme hemianopsie. Hemianopsie ontstaat wanneer de verwerking van visuele informatie in een van de beide hersenhelften al in een zeer vroeg stadium wordt onderbroken of gestoord, met als gevolg dat er blindheid optreedt voor een visueel halfveld. Het woord anopsie betekent dat er geen waarneming is, het woord hemi geeft aan dat er in een helft van het gezichtsveld geen waarneming optreedt en het woord homoniem betekent dat deze blindheid voor beide ogen hetzelfde is. Een homonieme hemianopsie voor het linker visuele veld wordt veroorzaakt door een beschadiging in de rechterhersenhelft. Mensen kunnen in het dagelijks leven veel hinder ondervinden van hemianopsie, zoals leesproblemen of het regelmatig stoten tegen voorwerpen of personen.

In *hoofdstuk 3* worden aan de hand van een systematische analyse van de bestaande literatuur twee revalidatiemethoden voor homonieme hemianopsie vergeleken. Een van deze twee therapieën, namelijk *restoratieve* therapie, heeft als doel om de verloren functies in de beschadigde visuele cortex zoveel mogelijk te herstellen. De aanname is dat, wanneer er nog voldoende hersencellen in het beschadigde gebied over zijn, stimulatie van deze cellen kan leiden tot nieuwe verbindingen tussen deze cellen, waardoor deels functieherstel optreedt. Deze stimulatie bestaat uit het langdurig en herhaald aanbieden van visuele prikkels op een beeldscherm. Omdat er aan de rand van een beschadigd gebied in het brein nog de meeste hersencellen overleefd hebben, treedt de functionele verbetering vooral op aan de rand van het visuele velddefect. Hierdoor zou het blinde gebied een paar graden kleiner worden.

De tweede revalidatiemethode die besproken wordt, is *scanning compensatie training*. Deze therapie is erop gericht om de patiënt grote oog- en hoofdbewegingen te laten maken in het blinde halfveld. Door met grote regelmaat grote oogbewegingen te maken in de richting van het blinde halfveld, compenseert de patiënt voor het verlies aan visuele informatie dat optreedt wanneer deze oogbewegingen niet worden

gemaakt. De aanname is dat door de oogbewegingen het *functionele* gezichtsveld wordt vergroot.

De conclusie van de vergelijking van de verschillende revalidatiemethoden is dat momenteel de voorkeur uitgaat naar scanning compensatie training boven restoratieve training. Een belangrijke reden hiervoor is dat er geen consensus bestaat omtrent de meetmethode waarmee de eventuele toename van het visuele veld moet worden vastgesteld. Bovendien is het maar de vraag of een toename van het gezichtsveld met slechts enkele graden voor de patiënt ook werkelijk leidt tot een vermindering van de klachten die het gevolg zijn van de gezichtsvelduitval.

In *hoofdstuk 4* worden verschillende revalidatiemethoden voor unilateraal neglect besproken. Kenmerkend voor neglect is dat stimulatie aan de zijde tegenover (contralateraal aan) de beschadigde hersenhelft niet wordt opgemerkt. Neglect komt meestal voor na een beschadiging van de rechterhersenhelft. Bij neglect is de feitelijke waarneming niet gestoord (zoals dat bij hemianopsie wel het geval is), maar is er een onvermogen om de aandacht te richten op de contralaterale zijde. Neglect wordt daarom gezien als een stoornis in de *representatie* van de ruimte. Er is relatief veel onderzoek verricht naar revalidatie van neglect. Slechts een klein deel van de onderzochte methoden, zoals visuele scanningtraining, is echter onderworpen aan een uitgebreide en gecontroleerde evaluatie van de korte- en langetermijn effecten in een grote klinische populatie. Sommige methoden zijn daarom weliswaar veelbelovend, maar nog onvoldoende bewezen.

In *hoofdstuk 5* wordt een patiënt (JS) beschreven met gestoorde herkenning van gezichten ten gevolge van een herseninfarct (CVA). Het opvallende is dat deze patiënt haar eigen familieleden veel slechter herkent dan beroemdheden. Wanneer mensen ten gevolge van een hersenbeschadiging gezichten van bekende personen, zoals familie en beroemdheden, niet goed kunnen herkennen, spreekt men van prosopagnosie. Mensen met prosopagnosie kunnen bekende personen wel herkennen aan hun stem, kleding of lichaamshouding. Hoewel mensen met prosopagnosie geen onderscheid kunnen maken tussen de gezichten van bekende en onbekende mensen, blijken ze wel een verhoogde huidgeleidingsrespons te hebben bij het zien van foto's van bekenden. Om deze reden wordt in de literatuur een onderscheid gemaakt tussen bewuste (overte) herkenning en onbewuste (coverte) herkenning van gezichten. Coverte

gezichtsherkenning bij prosopagnosiepatiënten is niet alleen aangetoond met behulp van toegenomen huidgeleidingsrespons, maar ook met behulp van elektro-encefalogram (EEG) en specifieke geheugentaken. Algemeen wordt aangenomen dat bij prosopagnosiepatiënten de overte herkenning gestoord is, terwijl de coverte herkenning nog intact is.

Het spiegelbeeld van prosopagnosie, namelijk intacte overte herkenning en gestoorde coverte herkenning, is door enkele wetenschappers waargenomen bij patiënten met het syndroom van Capgras. Mensen met Capgras delusie denken dat hun partner of hun naaste familieleden zijn vervangen door een dubbelganger. Ze vinden dat deze dubbelganger weliswaar dezelfde uiterlijke kenmerken heeft als de oorspronkelijke bekende, maar ze zijn er tegelijkertijd van overtuigd dat het deze bekende niet kan zijn. Wanneer foto's van bekenden en onbekenden worden getoond aan mensen met Capgras delusie, valt op dat ze geen verhoogde huidgeleidingsrespons laten zien bij het zien van bekende gezichten. Omdat deze huidgeleidingsrespons samenhangt met emotionele arousal, wordt door sommige onderzoekers aangenomen dat het 'gevoel' van herkenning ontbreekt bij mensen met Capgras delusie. Omdat dit gevoel juist bij de herkenning van de meest nabije familieleden of een partner het meest belangrijk is, wordt bij het zien van hen door de patiënt de conclusie getrokken dat het niet daadwerkelijk de personen zijn op wie ze lijken, maar dat ze zijn vervangen door een dubbelganger. Verondersteld wordt dat bij mensen met Capgras delusie de overte gezichtsherkenning intact is, terwijl de coverte herkenning gestoord is. Vandaar dat door sommige wetenschappers het syndroom van Capgras wordt gezien als het spiegelbeeld van prosopagnosie. In het onderzoek bij JS werden foto's van familieleden, beroemdheden en onbekenden getoond op een computerscherm.

Met behulp van reactietijden en huidgeleidingsrespons is onder meer onderzocht in hoeverre de overte en coverte gezichtherkenning gestoord waren. Uit het onderzoek bleek dat JS voor de herkenning van familieleden bijna twee keer zoveel tijd nodig had als voor de herkenning van beroemdheden. Bovendien maakte JS veel meer fouten bij de herkenning van familieleden dan bij de herkenning van beroemdheden. JS had echter wel een toename van de huidgeleidingsrespons bij het zien van familieleden. Dit is een aanwijzing dat de overte herkenning van familie gestoord is, terwijl de coverte herkenning nog intact is. In de discussie van dit

hoofdstuk wordt ingegaan op de vraag of de slechte herkenning van familieleden ten opzichte van beroemdheden gerelateerd is aan Capgras delusie of aan prosopagnosie.

In *hoofdstuk 6* worden de resultaten beschreven van een onderzoek naar vroege visuele verwerking van emotionele gezichtsuitdrukkingen en geconditioneerde gezichten bij 32 gezonde controles. Drie soorten stimuli weden aangeboden op een computerscherm: geconditioneerde boze gezichten, ongeconditioneerde boze gezichten en gezichten met een neutrale gezichtsuitdrukking. De geconditioneerde boze gezichten waren in een fase voorafgaand aan de meting gepaard aan een vervelend hard geluid. Bij de ongeconditioneerde boze gezichten en de neutrale gezichten was dit niet het geval. De verschillende gezichten werden zowel bewust als onbewust aangeboden. Hierbij werd gebruik gemaakt van een maskeertechniek. Deze techniek is gebaseerd op het principe dat wanneer een eerste stimulus extreem kort wordt aangeboden en onmiddellijk wordt gevolgd door een tweede stimulus, de eerste stimulus niet voldoende door de visuele cortex kan worden verwerkt om tot het bewustzijn door te dringen. Terwijl de stimuli werden aangeboden werd de hersenactiviteit gemeten met behulp van een afgeleide van het EEG: de event-related potential (ERP).

Uit de analyse van de ERPs viel af te leiden dat het eerste stadium van de verwerking van de onbewust aangeboden gezichten al na 140 ms optrad. Bewuste herkenning van gezichten en emotionele gezichtsuitdrukking door de ventrale route in de visuele cortex is normaliter pas in een later stadium van de ERPs te zien. Het vroege effect van de onbewuste aanbieding van gezichten wordt daarom waarschijnlijk niet veroorzaakt door visuele verwerking via de ventrale route, maar door projecties van subcorticale gebieden naar de visuele cortex. In termen van het model van LeDoux kan het vroege effect op het ERP na de onbewuste aanbieding van gezichten worden verklaard door verwerking via de ‘low road’. Volgens deze interpretatie kunnen subcorticale hersengebieden (in het bijzonder de amygdala) die betrokken zijn bij emotiegerelateerde visuele verwerking, de visuele cortex beïnvloeden in een stadium dat voorafgaat aan bewuste verwerking. Hierdoor kan de aandacht selectief gericht worden op emotioneel belangrijke stimuli, terwijl de aandacht voor minder belangrijke stimuli wordt verminderd. Opvallend was dat het ongeconditioneerde boze gezicht leidde tot een toename van de visuele aandacht, terwijl het geconditioneerde boze gezicht juist tot een verminderde visuele aandacht

leidde. Een mogelijke verklaring hiervoor is dat geconditioneerde stimuli niet bewust verwerkt hoeven te worden, terwijl ongeconditioneerde stimuli juist extra aandacht behoeven. In termen van het model van LeDoux: geconditioneerde boze gezichten worden primair via de 'low road' verwerkt, terwijl voor ongeconditioneerde boze gezichten een meer gedetailleerde analyse door de 'high road' nodig is. Dit vroege onderscheid tussen de geconditioneerde en ongeconditioneerde boze gezichten is ook een aanwijzing dat de subcorticale visuele verwerking nauwkeuriger is dan in het model van LeDoux wordt gesuggereerd. Immers, beide gezichten hebben globaal hetzelfde kenmerk, namelijk een boze gezichtsuitdrukking, maar het ene gezicht wordt 'herkend' als het geconditioneerde gezicht en het andere als het ongeconditioneerde gezicht.

De 32 deelnemers aan dit onderzoek vulden voorafgaand aan het experiment de Zelf-Beoordelings Vragenlijst in. Deze vragenlijst peilt zowel de tijdelijke gevoelens van angst en verhoogde autonome activiteit op een stressvolle situatie (toestandsangst) als een blijvende toestand van angst (angstdispositie), bijvoorbeeld door een tekort aan zelfvertrouwen. Bij personen met een relatief hoge score op de schaal voor angstdispositie was het effect van onbewuste aanbieding van gezichten sterker dan bij personen met een lage score op deze schaal. Tegelijkertijd was dit effect bij hoog-angstige personen minder specifiek: het verschil tussen het geconditioneerde gezicht en het ongeconditioneerde boze gezicht was minder groot dan bij de laag-angstige personen. Dit zou kunnen beteken dat mensen met een hoge angstdispositie emotiegerelateerde stimuli meer bewust verwerken en minder goed onderscheid maken tussen verschilleden soorten emotiegerelateerde stimuli dan mensen met een lage angstdispositie.

In *hoofdstuk 7* wordt een patiënt beschreven die ten gevolge van een CVA een beschadiging heeft van het onderste deel van de temporaalkwab en de amygdala in de rechterhersenhelft. Wanneer deze patiënt (FZ) foto's van angstige gezichten worden getoond, worden deze door hem systematisch geïnterpreteerd als verbaasde gezichten.

In een vergelijkbaar onderzoeksparadigma als in hoofdstuk 6 werden geconditioneerde angstige gezichten, ongeconditioneerde angstige gezichten en verbaasde gezichten bewust en onbewust aangeboden. Met behulp van ERPs werd onder meer coverte en overte herkenning van deze gezichten onderzocht. Hoewel bij FZ de overte, bewuste herkenning van angst gestoord is, zijn de vroege ERPs voor

angstige en verbaasde gezichten niettemin verschillend. Wanneer de gezichten bewust werden aangeboden, week het ERP-patroon van de angstige gezichten af van het ERP-patroon van de verbaasde gezichten. Dit is een aanwijzing dat de coverte herkenning van angst nog intact is, terwijl de overte herkenning van angst gestoord is. Wanneer de gezichten onbewust werden aangeboden, verschilden de ERP-patronen van de angstige en verbaasde gezichten niet meer van elkaar. Dit is een aanwijzing dat de coverte herkenning van angst, die optrad bij de bewuste aanbieding van gezichten, vooral gerelateerd is aan verwerking door de ventrale route van de visuele cortex.

In *hoofdstuk 8* worden de belangrijkste bevindingen samengevat en *hoofdstuk 9* bevat een discussie van deze bevindingen. In deze discussie wordt beargumenteerd dat de verschillen tussen ERPs van onbewust aangeboden stimuli vooral gerelateerd zijn aan visuele verwerking door subcorticale hersengebieden (met name de amygdala), terwijl de ERPs van bewust aangeboden stimuli vooral samenhangen met verwerking door de visuele cortex. Tegelijkertijd wil dit niet zeggen dat verwerking door subcorticale hersengebieden alleen gerelateerd is aan onbewuste visuele verwerking. Subcorticale gebieden zijn waarschijnlijk betrokken bij zowel bewuste als onbewuste informatieverwerking. De processen die samenhangen met verwerking door subcorticale gebieden wordt vooral beter zichtbaar gemaakt door stimuli onbewust aan te bieden, omdat de invloed van verwerking door de visuele cortex dan wordt geminimaliseerd.

In dit proefschrift wordt beargumenteerd dat subcorticale hersengebieden (in het bijzonder de amygdala), al in een zeer vroeg stadium van de informatieverwerking de visuele cortex beïnvloeden. Deze beïnvloeding resulteert in een toename van de visuele aandacht voor emotioneel belangrijke stimuli. Anderzijds leidt deze invloed tot een afname van de aandacht voor stimuli die emotioneel minder relevant zijn of voor stimuli die wel emotioneel relevant zijn maar die zonder tussenkomst van de visuele cortex verwerkt kunnen worden.

In het algemeen wordt aangenomen dat de snelheid van informatieverwerking via de subcorticale ‘low road’ ten koste gaat van de nauwkeurigheid. Een van de conclusies van dit proefschrift is dat verwerking van emotiegerelateerde visuele informatie door subcorticale hersengebieden via de ‘low road’ onder bepaalde omstandigheden nauwkeuriger is dan in het model van LeDoux wordt aangenomen. Anderzijds hangt de mate van onnauwkeurigheid van de visuele verwerking door

subcorticale hersengebieden samen met de mate waarin mensen in het dagelijks leven angst ervaren. Bij mensen met een hoge angstdispositie is de onnauwkeurigheid van de informatieverwerking via de ‘low road’ groter dan bij mensen met een lage angstdispositie.

Dankwoord

Dankwoord

Tot slot wil ik graag iedereen bedanken die mij heeft geholpen en ondersteund tijdens het schrijven van dit proefschrift.

Allereerst wil ik mijn promotores Anke Bouma en Wiebo Brouwer bedanken voor de toegewijde begeleiding en steun van de afgelopen jaren. Dank voor de vrijheid die ik van jullie kreeg en het vertrouwen dat jullie mij gaven bij het maken van soms lastige keuzes gedurende dit promotietraject. Ook bij tegenslagen wisten jullie mij te inspireren en te motiveren. Ik heb onze samenwerking als bijzonder plezierig ervaren, zowel op wetenschappelijk als op persoonlijk gebied, en ik ben blij dat we deze samenwerking kunnen voortzetten.

Dank aan de leden van de beoordelingscommissie: Edward de Haan, Aart Kooijman en Erik Scherder, voor het beoordelen van dit proefschrift.

Norbert Börger, Phillipa Butcher, Reint Geuze, Bauke de Jong, Berry Weijers en Andy Young wil ik bedanken voor hun inbreng bij het bedenken en uitvoeren van de experimenten en de hulp bij het analyseren en beschrijven van de resultaten.

Bij veel experimenten waren ook studenten betrokken. Nadine Weisscher, René Bax, Jorieke Wolterink, Céline Crajé, Hinke Drijver, Maartje Hofman en Evelien Kums, hebben met groot enthousiasme en inzet meegewerkt aan verschillende fasen van dit onderzoek.

Dank ook voor de technische ondersteuning door de medewerkers van de Instrumentatiedienst Psychologie: Joop Clots, Eise Hoekstra, Jaap Ruiter, Jan Smit, Hans Veldman en Pieter Zandbergen. Joop, bedankt voor het vervaardigen van het GSR apparaat, de ondersteuning bij de EEG metingen en je geduldige uitleg over technische zaken die mijn denkraam te boven gingen. Jan, bedankt voor het programmeren van vele computertaakjes, de gezelligheid en de discussies over de beste comedyseries van de BBC.

In het bijzonder wil ik mw. JS en dhr. FZ, bedanken. Jullie verleenden enthousiast en geduldig medewerking aan de experimenten. In dit proefschrift treden jullie op als anonieme personen, maar ik heb de samenwerking en het persoonlijke contact met jullie als zeer verrijkend ervaren.

Tom Manly, Ian Robertson en Chris Rorden wil ik bedanken voor de inspirerende en stimulerende samenwerking in Cambridge, die mij motiveerde om wetenschappelijk onderzoek en klinisch werk te combineren

Dank ook aan de collega's en oud-collega's van de afdeling Neuropsychologie van het UMCG voor alle interessante discussies en de gezelligheid van de afgelopen jaren. Ook de collega's van de afdeling Klinische en Ontwikkelingspsychologie aan de Grote Kruisstraat wil ik bedanken voor hun belangstelling en betrokkenheid. Om dezelfde reden wil ik ook de collega's van Visio Noord-Nederland bedanken. Lies, bedankt voor je doorzettingsvermogen om het neuroteam in Haren op de kaart te zetten. Ik hoop dat we het team nog verder kunnen opbouwen en nog veel gezamenlijk onderzoek kunnen doen.

Brecht Griffioen en Evelien Kums, fijn dat jullie mijn paranimfen wilden zijn en mij veel werk uit handen hebben genomen bij de organisatie van de feestelijkheden. Brecht en Niels, bedankt voor het gastvrij beschikbaar stellen van jullie logeerkamer op de momenten dat er hard doorgewerkt moest worden. Evelien, ik ben blij je als collega te hebben en hoop dat we samen nog meer onderzoek kunnen doen.

Ik wil mijn ouders, broers, zussen en schoonfamilie bedanken voor hun belangstelling en steun, zeker in de laatste fase van het schrijven. Helmich, Justus en Gabriël, bedankt voor jullie vrolijkheid en geduld. Ik ben trots op jullie.

Liesbeth, zonder jou was dit proefschrift er niet gekomen. In alle fasen heb je me gesteund, geholpen en veel ruimte gegeven – ook als ik soms mopperig thuiskwam na een kritische brief van een reviewer. Je hebt in de achterliggende periode veel gedaan en je hebt ook veel moeten nalaten om dit mogelijk te maken. Mijn grootste dank is daarom voor jou.

Publications

Publications:

Bouwmeester, L. Heutink, J. & Lucas, C. (2007) The effect of visual training for patients with visual field defects due to brain damage. A systematic review. *Journal of Neurology, Neurosurgery and Psychiatry, 78*, 6, pp. 555 – 564.

Heutink, J. (2006). Gezichtsvelduitval bij niet-aangeboren hersenletsel. In: B.J.M. Melis-Dankers & C.P.Mebis (Eds.) Visuele training bij niet aangeboren hersenletsel. Huizen: Vereniging voor Revalidatie van Slechtziendheid. ISBN-13: 978-90-806736-9-4

Heutink, J., Brouwer, W., Jong, B. de, & Bouma, A. Conscious and unconscious processing of fear after right amygdala damage - a single case ERP study. *(Manuscript submitted for publication)*

Heutink, J., Brouwer, W.H., Kums, E., Young, A.W. & Bouma, A. Disproportionate impairment of recognition of close family members:a case of selectiver prosopagnosia of a mild variant of Capgras delusion? *(Manuscript in preparation).*

Heutink, J., Brouwer, W.H., Wijers, A.A., Börger, N.A. & Bouma, A. Differential modulations of P1 and N170 in conscious and unconscious processing of emotional faces and their relationship to individual differences in anxiety. *(Manuscript in preparation).*

Manly, T., Heutink, J., Davison, B., Gaynord, B., Greenfield, E., Parr A., Ridgeway, V. & Robertson (2004). An electronic knot in the handkerchief: "Content free cueing" and the maintenance of attentive control. *Neuropsychological Rehabilitation 14,* 1-2, pp. 89-116.

Robertson, I.H. & Heutink, J. (2002). Rehabilitation of Unilateral Neglect. In: W.H. Brouwer et al. (Eds.) Neuropsychological Rehabilitation: a Cognitive Approach. Amsterdam: Boom.

Manly, T., Davison, B., Heutink, J., Galloway, M. & Robertson, I.H. (2000). Not enough time or not enough attention? Speed, error and self-maintained control in the Sustained Attention to Response Test (SART). *Clinical Neuropsychological Assessment, 3*, 167 – 177.

Rorden, C., Heutink, J., Greenfield, E. & Robertson, I.H. (1999). When a rubber hand 'feels' what the real hand cannot. *NeuroReport 10*, pp. 135 – 138.

Scholarships and awards:

2004 'Young Researcher Award' at the First Congress of European Societies of Neuropsychology in Modena, Italy.
2003 Award for best poster presentation at the Endo-Neuro-Psycho Meeting in Doorwerth.
2002 Award for best poster presentation at the Heymans Symposium in Groningen.
1997 VSB-scholarship for research or a study abroad.

Curriculum vitae

Curriculum vitae

Joost Heutink werd op 28 september 1973 te Zwolle geboren en groeide op in Genemuiden. In 1992 behaalde hij het VWO diploma aan het Johannes Calvijn Lyceum te Kampen. Datzelfde jaar begon hij met de studie psychologie aan de Rijksuniversiteit Groningen. In augustus 1997 studeerde hij af in de doctoraalrichting Klinische psychologie met een bijzondere belangstelling voor de neuropsychologie.

Van 1997 tot 1998 werkte hij bij de Cognition and Brain Sciences Unit van de Medical Research Council te Cambridge, waar door het onderzoek naar de relatie tussen ruimtelijke cognitie en volgehouden aandacht zijn enthousiasme voor het verrichten van patiëntgebonden onderzoek werd aangewakkerd. Dit onderzoek zette hij in 1999 voort aan de Universiteit van Turku te Finland, waar hij als gastonderzoeker werkte. Sinds 2000 werkt hij bij de afdeling Klinische en Ontwikkelingspsychologie van de faculteit Gedrags- en Maatschappijwetenschappen van de Rijksuniversiteit Groningen, waar hij momenteel onderzoek verricht en onderwijs geeft op het vakgebied van de klinische neuropsychologie. Van 2005 tot 2007 werkte hij ook als docent van het vak Assessment en Diagnostiek aan de faculteit Gedragswetenschappen aan de Universiteit Twente. Sinds 2004 is hij als neuropsycholoog werkzaam bij Visio Noord-Nederland te Haren. In zijn werkzaamheden bij Visio is hij vooral betrokken bij volwassen patiënten met een gestoorde visuele waarneming ten gevolge van een neurologische aandoening.

In zijn vrije tijd verdiept hij zich in Russische ikonen. Hij was nauw betrokken bij de oprichting van het Ikonenmuseum Kampen in 2005, waar hij sindsdien als gastconservator een aantal exposities verzorgde en meewerkte aan diverse publicaties. In 2006 schreef hij samen met kunsthistorica Désirée Krikhaar het boek Beelden van het Licht, dat werd uitgegeven door Kok Kampen. Naast zijn liefde voor ikonen is hij actief als musicus. Hij is kerkorganist en cantor en zingt bij het internationaal gerenommeerde vocaal ensemble The Gents, waarmee hij regelmatig op nationale en internationale podia optreedt.

Joost Heutink is sinds 1998 getrouwd met Liesbeth van Es. Ze hebben samen drie kinderen: Helmich (2000), Justus (2002) en Gabriël (2006).