Fakultät für Erziehungswissenschaft, Psychologie und Bewegungswissenschaft
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The blinds' brain – a study in plasticity

Vorgelegt von

Diplom-Psychologin

Corinna Klinge

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Contents

Summary

In everyday life, blind individuals are at a disadvantage as the majority of aspects in our society are presented visually. In order to be able to find themselves around despite this grave disability, blind people show extraordinary capabilities in other sensory domains. These superior abilities have been tested by scientists, and were shown to often go in hand with additional activations of the visual cortex, which turned out to be functionally relevant for the blinds' augmented performance. Research done so far focussed on sensory tasks and some more complex cognitive tasks. However, emotional processing had never been studied in the blind.

In the present work I therefore set out to investigate auditory emotional processing in connatally (born) blind humans. Apart from a behavioural advantage in an emotion- and a phoneme-discrimination task, I found blind individuals to show increased amygdala activations when compared to sighted matched controls, at least for angry and fearful stimuli. In a follow up study, I aimed at distinguishing two different explanations for this pattern of results. I therefore studied professional actors that were matched with blind participants, assuming they had gained a great auditory expertise during their training. In this later study, I found support for the notion that the superior behavioural performance and the augmented amygdala activation in the blind are driven by different mechanisms. While behavioural performance seems to be modulated by training in that very sensory domain, it is blindness per se, i.e. the deprived sensory state that drives plastic changes within the amygdala.

On top of these findings I was able to differentiate between different pathways via which the additional activation of the visual cortex in the blind in response to auditory stimuli could come about. Data showed clear support for increased strength of cortico-cortical connections (between primary auditory and visual cortices) in the blind while thalamo-cortical pathways (auditory thalamus - visual cortex) did not differ in strength between the two groups.

Foreword

“If you could climb to the top of the world, we also can overcome our borders and show to the world that the blind can equally participate in society and are able to accomplish great things.“

E-mail excerpt from Sabriye Tenberken

What seems almost impossible or exaggerated was put into action by Sabriye Tenberken, a blind school teacher in Tibet who invited Erik Weihenmayer, a famous blind mountaineer, to climb the Lhakpa Ri with her and some blind pupils (“BLINDSIGHT - The Film,” n.d.). In Tibet, blind individuals are stigmatized as possessed by demons. People believe that blindness is a punishment for something bad one has done in a former life. Therefore, families hide or cast out their blind children. The documentary “blindsight” is about Sabriye and her school for the blind in Tibet who not only teaches the children educational issues but also confidence. Confidence to achieve just about anything they dream of.

In this dissertation, I will describe the work I carried out during my PhD studies. This work involved working with connatally blind (blind from birth) and sighted human volunteers plus sighted professional actors – using auditory paradigms in combination with functional magnetic resonance imaging (fMRI) – and focussed on the plasticity of brain mechanisms that underlie the enhanced capabilities the blind demonstrate in their spared modalities. I will start with an introduction on blindness and cortical plasticity, sensory processing of auditory and visual information and the responsible brain structures, including the amygdala (chapter 1), after which I will briefly describe my research questions. General information on the method

of fMRI – also including data preprocessing and analysis steps – will be given in chapter 2. In chapters 3 to 6, the four studies I carried out will be illustrated, all including the relevant introductions, methods, results, and brief summaries of the findings. I will then discuss the results and the implications these have on the present knowledge (chapter 7) and will finish with a conclusion that includes a very brief outlook of open issues (chapter 8).

1 Introduction

1.1 Blindness – from cause to consequence

Blindness is defined as a condition in which the individual lacks vision. This lack can be due to diseases, traumata or genetic factors and can have effects of differing strength both of which I will describe briefly in the following. Different extents of visual loss can be distinguished. *Total blindness* includes the inability to see anything, not even light. *Blindness* on the other hand can involve not seeing anything but still having the ability to perceive light and its source. Further, so-called *low vision* entails reduced vision even when using the best possible correction available. Legally, blindness is assessed through visual acuity of the stronger and maximally corrected eye. If the stronger eye only has a visual acuity of 1/50 or less, or if visual faculty is disturbed in any other way equal to a decreased visual acuity, the person is considered and diagnosed as blind. Of those termed legally blind, approximately ten percent have no vision whatsoever.

In this work, I describe findings in a connatally blind group that I compared to matched controls under experimental conditions. All blind participants were totally blind, except for one who had residual light perception. The reasons for their blindness ranged from degenerated optic nerves, over retinoblastoma and prenatal retinitis to retinopathy of prematurity, and Leber's congenital amaurosis (see Table A1 in Appendix 1 for detailed information on the participants). For a rough understanding of these causes the meaning behind these diagnoses will briefly be explained.

Retinoblastomas are rapidly growing cancers in retinal cells (Lohmann, 2010). These can be either heritable (due to a mutation on chromosome 13, called RB1) or non-genetic. In only one of three cases both eyes are affected. The two eyes may be affected differently, regarding the size and number of tumours which also influences the choice of treatment. In

children, the heritable form of retinoblastoma occurs in very early fetal development and affects both eyes in the majority of all cases, as opposed to adult cases of emerging retinoblastomas.

Retinopathy of prematurity (ROP) can affect prematurely born babies whose retina is often not yet fully vascularized. This eye disease is most likely caused by disorganized growth of retinal blood vessels (fibrovascular proliferation) which may result in scarring and retinal detachment. Preterm babies, especially babies with low weight, are in general at risk for ROP, with oxygen toxicity and relative hypoxia contributing to its development (Sylvester, 2008).

Retinitis pigmentosa (RP) is a genetic eye disease often found in adults, though rarely also in very young children. This can also happen neonatally (Stone, Maslim, Fawzi, Lancaster, & Heckenlively, 2001). There does not seem to be a standard progression - cases differ from one another. RP is considered one form of progressive retinal dystrophy, concerning the photoreceptors or the retinal pigment epithelium of the retina which leads to a progressive loss of vision. The disease starts off with altered night vision (‘night blindness’), followed by a reduced peripheral visual field (‘tunnel vision’) to finally end in the loss of central vision.

Leber's congenital amaurosis (LCA) is also one of the heritable eye diseases, appearing at birth or the following first months (Cremers, van den Hurk, & den Hollander, 2002). Beside these facts, there is no uniform progression of the disease and several genes seem to be involved in it. The disease is mostly associated with a nystagmus, slowed papillary responses, and in more drastic cases with visual loss and blindness.

In daily life, vision presents a crucial form of perception as many aspects are vision-dominated in our world, such as road signs, information forms, TV, books, tickets, etc.

Schools and universities are conceived for sighted, as well as pedestrian crossings, train display panels or lists of food ingredients. Only rarely, and mostly in bigger cities, one notices a beeping traffic light, certain corrugations of the pavement on a train's platform or Braille writing, the blinds' way of written language. Thus, for blind people every day life in our society is harder to master, and they depend on helpful others, showing them the way, reading information to them, handing them the right item during shopping or taking them from one place to another, to name just a few examples. When talking to blind people, their disability is often perceived as a handicap, but they are also astonished and shocked at how little the sighted use their other senses. For them, it is much easier to recognize something just by grasping it for a second, or recognizing someone by his pace, voice or smell (personal communication), as they have to rely on non-visual cues in order to efficiently interact with others and the environment. As one participant stated: "While we're treated as disabled it is really you who need help because we only lack vision whereas you are weak in lots of different things."

The blinds' augmented behavioural performance in their spared modalities has repeatedly also been shown in diverse experimental tasks. The blinds' greater expertise in analyzing for example auditory information is reflected in various outstanding auditory capabilities, such as pitch discrimination (Gougoux et al., 2004), verbal memory (Amedi, Raz, Pianka, Malach, & Zohary, 2003; Röder, Rosler, & Neville, 2001), auditory localization skills (Ashmead et al., 1998; Gougoux, Zatorre, Lassonde, Voss, & Lepore, 2005; Lessard, Pare, Lepore, & Lassonde, 1998; Muchnik, Efrati, Nemeth, Malin, & Hildesheimer, 1991; Röder et al., 1999; Voss, Gougoux, Zatorre, Lassonde & Lepore, 2004), and speech perception (Muchnik et al., 1991; Niemeyer & Starlinger, 1981; Röder, Stock, Bien, Neville, & Rosler, 2002), in all of which they outperform sighted people. Blind individuals show superior performance to sighted controls in several other modalities as well. They show finer tactile discrimination thresholds (Alary et al., 2008; Alary et al., 2009; Goldreich & Kanics, 2003;

Van Boven, Hamilton, Kauffman, Keenan, & Pascual-Leone, 2000), enhanced spatial navigation skills (Fortin et al., 2008), and enhanced olfactory identification abilities (Cuevas, Plaza, Rombaux, De Volder, & Renier, 2009; Rosenbluth, Grossman, & Kaitz, 2000).

These superior performances have been found to be frequently accompanied by additional activations of the occipital cortex (OCC), as shown previously in electro-encephalogram (EEG)- and imaging studies in auditory tasks [e.g. pitch changes (Kujala et al., 1995), auditory localization (Gougoux et al., 2005; Leclerc, Saint-Amour, Lavoie, Lassonde, & Lepore, 2000; Voss, Gougoux, Zatorre, Lassonde, & Lepore, 2008; Wanet-Defalque et al., 1988; Weeks et al., 2000), auditory imagery (De Volder et al., 2001) speech processing (Burton & McLaren, 2006; Gougoux et al., 2009; Röder et al., 2002), auditory object recognition (Arno et al., 2001), auditory motion perception (Poirier et al., 2006), and auditory change detection (Kujala et al., 2005)], memory tasks (Amedi et al., 2003; Raz, Amedi, & Zohary, 2005), mental imagery (De Volder et al., 2001), mental rotation (Röder, Rosler, & Hennighausen, 1997), during the use of visual-to-auditory sensory substitution devices (Arno et al., 2001; Amedi et al., 2007; Collignon, Lassonde, Lepore, Bastien, & Veraart, 2007), in tactile tasks such as in Braille reading and tactile discrimination (Büchel, Price, Frackowiak, & Friston, 1998; Burton et al., 2002; Burton, 2003; Cattaneo et al., 2008; Pietrini et al., 2004; Pons, 1996; Röder et al., 1997; Sadato et al., 1996; Uhl, Franzen, Lindinger, Lang, & Deecke, 1991; Wanet-Defalque et al., 1988), and during the use of visual-to-tactile sensory substitutive devices (Ptito & Kupers, 2005). Note however, that a relative decrease in OCC activation in the blind under lower attentional conditions in comparison to more demanding tasks has also been reported (Ruff et al., 2006; Weaver & Stevens, 2007).

These changes in cortical activation patterns have been interpreted as a result of cortical plasticity. The proposal that the brain and its functions may not be fixed throughout adulthood was first made by William James (1950) but at that time the idea was largely neglected. It was

only in the 1920ies that the idea of the plastic brain was rediscovered when Paul Bach-y-Rita invented a visual-to-tactile sensory substitution device, allowing blind people to "see" (Doidge, N., 2007). Patients sat in an electrically stimulated chair with a large camera installed behind it scanning the area and sending electrical signals of the image to 400 vibrating stimulators on the chair against the patient's skin. This perception could only be possible because the brain learned something new and adapted to new input. The brain's capacity to adapt implied that it possessed plasticity. Michael Merzenich was one of the first to provide experimental evidence for plastic changes within the monkey's brain. In three experiments he could show that a) after the removal of one finger, the representation of the other fingers expanded into the now "unused representation of the removed digit" and b) rewarding a certain motor behaviour enlarged the representation of the limp used in the task with time (Merzenich & Jenkins, 1993). Plasticity is thus a very helpful property for the deprived organism to adapt to the changing environment. Plastic (cortical) changes can however also lead to more or less severe maladjustments, such as for example tinnitus, phantom limbs pain, and focal distonia (the "musicans' cramp"; Lim, Altenmüller, & Bradshaw, 2001), to name just a few. These maladjustments are expressions of cortical plasticity as well, caused by disorganized or degraded brain maps. They are in stalk contrast to the "good" cortical plasticity described above in which additional brain parts (e.g. the OCC) take over tasks in order to improve performance and adaptation to the environment.

Based on the findings mentioned above, it has been hypothesized that the recruitment of the OCC in the blind may account for their exceptional abilities, e.g. in performing auditory spatial tasks (Cohen et al., 1997; Gougoux et al., 2005; Hamilton & Pascual-Leone, 1998; Hyvärinen & Hyvärinen, 1979; Röder et al., 1999). Although these associations between OCC activation and augmented performances in the blind were found and correlative associations have been reported (e.g. Gougoux et al., 2005), very few studies were able to provide direct experimental (Amedi, Floel, Knecht, Zohary, & Cohen, 2004; Cohen et al., 1997; Collignon

et al., 2007; Collignon, Davare, Olivier, & De Volder, 2009; Kupers et al., 2007; Merabet et al., 2009; Wolbers, Zahorik, & Giudice, 2010) and clinical evidence (Hamilton, Keenan, Catala, & Pascual-Leone, 2000) for causal links between OCC recruitment and compensatory abilities in blind humans. These studies and proposed underlying mechanisms will be described in more detail in chapter 5. The functional relevance of OCC in the blind has thus been established for a number of subfunctions in both the tactile and the auditory modality.

1.2 Auditory processing and the primary auditory cortex

In the following I will give a brief explanation of how sound is processed within the human nervous system. Sound reaches humans via the ear, the input region to further processing within the brain. Humans can hear sound between ~20-20.000 Hz (oscillations per second). Having travelled through the outer, middle, and inner ear, sound information is transformed from mechanical waves into an electric neural signal in the Organ of Corti which communicates with dendrites of primary auditory neurons. The latter are bundled in the auditory (cochlear) nerve which joins the vestibular nerve to then form the vestibulocochlear nerve. Information is transferred to the thalamus through the lateral lemniscus, passing through intermediate stations such as the cochlear nuclei (where it crosses to the contralateral side), the superior olivary complex within the brainstem (that allows localizing sounds on the azimuthal axis, based on auditory interaural delays and intensity cues that it gets from both ears), and the inferior colliculus in the midbrain. The inferior colliculus is subdivided into a dorsal part that receives both auditory and somatosensory input and the central nucleus that is involved in auditory localization. Within the thalamus, an oval structure that lies within the diencephalon and conveys sensory input to primary sensory areas, the medial geniculate nucleus (MGN) presents a major auditory relay station. The MGN is composed of at least 3 subdivisions, of which the principal nucleus receives auditory input while the other components receive multimodal input. The principal nucleus is organized tonotopically and

cells are sharply tuned to specific frequencies (Kandel, Schwartz, & Jessell, 2000; Pinel, 2001).

From the MGN, information is relayed to the cortex, more specifically to the primary auditory cortex (A1) that is located on the transverse gyrus of Heschl within the temporal lobe. This cortical region allows the sensation of basic auditory characteristics such as pitch. The primary auditory cortex is composed of functional columns (Schreiner, 1992): Neurons within the same column process sounds of the same frequency. Further, they are organized tonotopically, like all the previous stages in auditory processing mentioned before: auditory neurons are spatially arranged in an orderly map – according to the auditory frequencies they process. There is increasing evidence that a distinction into two different pathways with distinct functions ("where" and "what"; like in the visual cortex) can also be found in the auditory cortex (e.g. Kaas & Hackett, 1999; Rauschecker & Tian, 2000). Acoustic signals can be distinguished and recognized as speech, music etc. when processed by Wernicke's area, in the auditory association cortex within the temporal lobe. Besides A1 and Wernicke's area, several other brain areas also process sound information; these are however not relevant for the present thesis.

1.3 Processing of emotional prosody

Besides semantic content, speech contains different types of vocal information, such as the identity of speakers, their ages, but also their emotional state. In this regard, the term "prosody" refers to the rhythm, intonation, and stress of speech. It not only informs the listener about whether an utterance is a statement or a question and whether the speaker is being ironic but also about his or her emotional state. During speech, acoustic parameters are modified through the influence of autonomic effects, specific patterns of muscular contraction, breathing speed etc. this way, voices are directly influenced by the speaker's affective state.

Emotional prosody, the affective speech melody, includes acoustic parameters of speech such as mean segment and pause duration, amplitude, mean fundamental frequency (f0; = frequency of glottal vibration; closely related to what we perceive as pitch), and f0 variation, allowing the listener to infer the speaker's affective state (Banse & Scherer, 1996; Kappas, Hess, & Scherer, 1991; Scherer, 1981; Scherer, 1986; Scherer, 1995). Structures involved in speech perception range from bilateral auditory regions of the superior temporal cortex posterior and anterior to Heschl's gyrus, extending inferiorly to the middle and anterior parts of superior temporal sulcus (for review see e.g. Scott & Johnsrude, 2003). FMRI studies further suggest that the amygdala and insula may also be important structures implicated in the processing of vocal emotions (Fecteau, Belin, Joanette, & Armony, 2007; Sander & Scheich, 2001; Sander et al., 2005).

1.4 Visual processing and the primary visual cortex

I will briefly describe how visual stimuli are processed within the human brain, leaving out visual processing within the eye as it is not relevant for this thesis. Visual information reaches the visual cortex through the optic radiation which connects the lateral geniculate nucleus (LGN) to the primary visual cortex, also called V1 or striate cortex. The LGN is the major thalamic terminus for input into the visual cortex. In the LGN, a complete retinotopic representation of the contralateral visual field is created. Information from the two eyes remains segregated. V1 has six functionally distinct layers, with layer 4 receiving most of the visual input from the LGN. Visual information is processed contralaterally. From V1 onwards, visual information flows through a cortical hierarchy, including areas V2, V3, V4, and V5/MT. The primary visual cortex is situated at the posterior region of the OCC. In V1, neurons only fire when stimulated by a certain arrangement of active presynaptic cells (e.g. stimulated by a bar of light in a certain orientation). Similarly, basic information about e.g. colour is processed here and in V4. Secondary visual areas (V2-V5), also named extrastriate

visual cortex, process other visual primitives. As visual information is transferred onwards through visual hierarchy, the complexity of the processed stimulus features increases. While V1 responds to e.g. a line of light in a specific location and orientation, neurons in the lateral occipital complex respond selectively to complete objects, and other parts in the visual association cortex respond selectively to faces from a particular species or motion (V5). As complexity increases, the level of specialization of processing is augmented. From this point on, visual processing happens in parallel in two separate pathways, the dorsal ("where"; spatial localization) and the ventral ("what"; object recognition) pathway ("two streams hypothesis"; Mishkin & Ungerleider, 1982; Schneider, 1969; Ungerleider, Courtney, & Haxby, 1998). The dorsal pathway connects V1 to the posterior parietal cortex, while the ventral pathway leads to the inferior temporal gyrus (Kandel et al., 2000; Pinel, 2001).

1.5 The amygdala

The amygdala is a relatively small, phylogenetically old structure positioned in the anterior medial part of the temporal lobe (Figure 1). It comprises cortical grey matter and subcortical nuclei (Swanson & Petrovich, 1998), consisting of several nuclei with unique connections and functions each (e.g. Ball et al., 2007; LeDoux, 2007; Roy et al., 2009). The amygdala is recognized as a crucial part of the limbic system, being one of the core structures involved in affective processing. It receives important afferent information from all sensory modalities and relays it to its major output region, the central nucleus (McDonald, 1998). Subdivisions of the amygdala can be distinguished through histological techniques

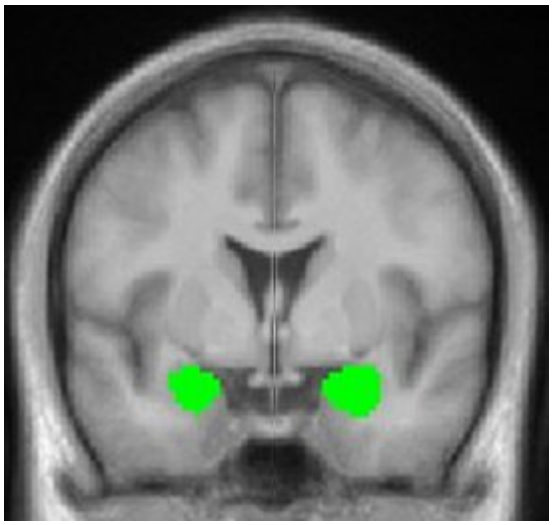

Figure 1. Coronal view of the amygdalae depicted using a standard amygdala mask (FSL) on a mean structural image.

(LeDoux, 2007) and most recently also through high resolution fMRI (Ball et al., 2007). Despite this potentially clear partitioning of the amygdala, there is an ongoing debate on the partitions and their names (LeDoux, 2007). Further, these subregions differ in exact location interindividually (Ball et al., 2007). Hence, caution has to be taken when talking about the amygdala as a whole.

A century ago, researchers found the removal of the temporal lobe, including the amygdala, to lead to dramatic changes in behaviour, especially in emotional behaviour in monkeys (Kluver & Bucy, 1939). Later studies with human amygdala lesion patients reported an impaired recognition of fearful/negative facial cues (Adolphs, Tranel, Damasio, & Damasio, 1994; Adolphs et al., 1999; Atkinson, Heberlein, & Adolphs, 2007; Broks et al., 1998; Calder, 1996; Tsuchiya, Moradi, Felsen, Yamazaki, & Adolphs, 2009) and an impaired recognition of threatening auditory cues (Scott et al., 1997), such as scary and sad music (Gosselin, Peretz, Johnsen, & Adolphs, 2007) and paralinguistic signals (Scott et al., 1997). When intact, the amygdala was found to be active under negative emotional conditions (Breiter et al., 1996; Morris et al., 1996) and elicited feelings of fear when stimulated electrically (Halgren, Walter, Cherlow, & Crandall, 1978). Consequently, it was considered responsible for fear processing (Davis, 1992; LeDoux, 1995; Phan, Wager, Taylor, & Liberzon, 2002). This view however has changed, as findings of amygdala activation to other emotions were also reported (e.g. Blood & Zatorre, 2001; Hamann & Mao, 2002; Liberzon, Phan, Decker, & Taylor, 2003; Pichon, de Gelder, & Grèzes, 2009; Wiethoff, Wildgruber, Grodd, & Ethofer, 2009; Yang et al., 2002). Researchers found the amygdala to process emotional stimuli in general, including emotional voices (Fecteau et al., 2007; Johnstone, Reekum, Oakes, & Davidson, 2006; Morris, Scott, & Dolan, 1999; Sander & Scheich, 2001; Sander et al., 2005; Schirmer et al., 2008), linguistic threat (Isenberg et al., 1999), olfactory and gustatory stimuli (Lascano, Hummel, Lacroix, Landis, & Michel, 2010 and Lundström,

Boyle, Zatorre, & Jones-Gotman, 2008, respectively), as well as emotional music (Blood & Zatorre, 2001; Koelsch, Fritz, & Schlaug, 2008).

Paralleling findings of amygdala activations in healthy humans, lesion studies have found amygdala lesions to lead to certain failures, such as an impaired recognition of scary music, as opposed to normal recognition of happy (Gosselin et al., 2007) or sad music (Gosselin et al., 2005), impaired loss aversion (De Martino, Camerer, & Adolphs, 2010; Talmi, Hurlemann, Patin, & Dolan, 2010), and impaired direction of the gaze towards the eye region (which is most informative in some emotions; mostly for fear; Adolphs et al., 2005). The same authors found that - when asked to identify a facial emotion with the additional instruction to pay attention to the eyes - the same patient suddenly showed normal performance. The authors concluded that impairment in recognizing emotions stem from an inability to make normal use of information from the eye region of faces. Additionally, performances in diverse tasks have also been found to be unaffected by a lesioned amygdala: recognition of happy facial cues (Adolphs et al., 1999; Adolphs & Tranel, 1999), affective evaluation of negative emotional scenes (Hamann, Cahill, McGaugh, & Squire, 1997), and rapid detection and unconscious processing of fearful faces (Tsuchiy et al., 2009). Even normal recognition of individual facial emotions has been reported (Hamann & Adolphs, 1999).

Besides fear conditioning which I will not go further into, visually transferred emotions have been studied most in humans (e.g. Gläscher, Tuscher, Weiller, & Büchel, 2004; Hariri, Tessitore, Mattay, Fera, & Weinberger, 2002; Morris et al., 1996; Reinders et al., 2006; for meta-analyses on this topic see Costafreda, Brammer, David, & Fu, 2008; Phan et al., 2002), whereas researchers have only recently begun to also investigate acoustically transferred emotions in more detail. While some researchers found emotional sounds to lead to amygdala activations (e.g. Bach et al., 2008; Fecteau et al., 2007; Johnstone et al., 2006; Morris et al.,

1999; Phillips et al., 1998; Sander & Scheich, 2001; Sander et al., 2005; Schirmer et al., 2008), others did not (Bach et al., 2008; Buchanan et al., 2000; Ethofer, Anders, Wiethoff, et al., 2006; Grandjean et al., 2005; Jäncke, Buchanan, Lutz, & Shah, 2001; Mitchell, Elliott, Barry, Cruttenden, & Woodruff, 2003).

Mixed results may be due to the lack of differentiating between different subdivisions of the amygdala. Based on all findings, the amygdala's task may be the recognition of salient relevant events allowing for efficient reorientation of attention towards them (Anderson & Phelps, 2001; Amaral, 2002; Gläscher & Adolphs, 2003; Sander, Grafman, & Zalla, 2003). Experimental support for this hypothesis has been provided in different contexts: Schirmer et al. (2008) found amygdala activation in response to emotional prosody in pseudo words to correlate positively with social orientation. Andersen & Phelps (2001) and Vuilleuimier, Richardson, Armony, Driver, & Dolan (2004) showed amygdala activation to be associated with enhanced attentional capture and the processing of stimuli that are of high relevance to an individual's goals or needs.

As already stated above, subdivisions of the amygdala have only recently been studied and identified. Thus, former literature could not differentiate between partitions. In the following I will therefore treat the amygdala as one structure and will not differentiate between subparts.

1.6 Research questions

Despite the wealth of evidence for plasticity-induced behavioural performance advantages of the blind mentioned above, there are still many unsolved topics, some of which will be investigated in this thesis. More specifically, this thesis aims to answer the following questions. 1. Does augmented auditory performance in the blind also apply to the recognition of acoustically transferred emotions? 2. If so, is this due to blindness per se (i.e. deprivation-

induced) or due to stronger sensory training (expertise; i.e. use-dependent)? 3. Do we find plasticity effects in the amygdala, an evolutionary old structure important for emotional processing? 4. What mechanisms are underlying the additional OCC activations caused by auditory stimulation in the blind?

Before moving on to describe the work aimed to answer these questions, I will briefly describe the methods that were used in this endeavour. I will then describe study 1, which was carried out in order to provide validatd stimulus material, before moving on to study 2, which answered questions 1-3, will go on with study 3, answering question 4, and will then finish with study 4, for more answers to question 2.

2 Methods

2.1 MRI, fMRI, and the physiology behind it

Most data of the present work were obtained through brain imaging via the method of functional magnetic resonance imaging (fMRI). The following section will therefore briefly describe some of the basics of fMRI and will then move on to the general processing of fMRI data.

Magnetic resonance imaging: MRI is an imaging technique that works non-invasively. It measures the response of hydrogen molecules to a perturbation in a magnetic field. In order to gain an MRI signal, the body - or the head in my studies - of a volunteer has to be placed in a magnetic field which aligns all the originally desynchronized electrically charged nuclei. Brief high frequency pulses (radio frequency, RF) are then applied perpendicularly, causing protons to precess in synchrony. Once the RF pulse is turned of, protons relax and consequently fall out of synchrony. This falling out of synchrony (‘dephasing’) of rotating protons is measured and presents the MRI signal. Depending on the surroundings, the signal

of these nuclei varies in strength, enabling us to differentiate between grey matter, white matter, and cerebral spinal fluid in structural images.

Functional magnetic resonance imaging: In this thesis, fMRI was used, an MRI-based technique that allows us to indirectly measure the activity of the brain. It was introduced in 1992 when several laboratories independently identified a mechanism that could be used for such non-invasive measurement (Bandettini, Wong, Hinks, Tikofsky, & Hyde, 1992; Frahm, Bruhn, Merboldt, & Hänicke, 1992; Kwong et al., 1992; Ogawa et al., 1992). FMRI detects changes in blood flow and oxygenation occurring in response to neural activity. Underlying is the phenomenon that a brain area has an increased metabolism when active. In order to meet this augmented demand, blood flow in this area increases as oxygen is delivered by haemoglobin in capillary red blood cells. In the process, the concentration of oxygenated haemoglobin increases in relation to deoxygenated haemoglobin. The two oxygenation states have different magnetic properties: When oxygenated, haemoglobin is diamagnetic (opposed to the magnetic field), while it is paramagnetic (attracted by the magnetic field) when deoxygenated. This difference leads to small, detectable differences (inhomogeneities) in the magnetic field, and therefore in the fMRI signal - the blood oxygen level dependent (BOLD) response. Using fMRI, one can detect these changes, locate areas that are active under certain conditions or tasks, and visualize these on so-called activation maps. Activation maps depict each voxel (volume pixel; the smallest recording unit in fMRI) and its response to a certain stimulus; to be more specific: they show how closely its time-course resembles the expected time-course given certain stimulation.

BOLD and the haemodynamic response function: The BOLD response consists of different stages: an initial dip when blood oxygenation is slightly decreased at the beginning of neural activity, followed by a period of increased (and overcompensating) blood flow which peaks at ~6 seconds to eventually fall back to baseline with an undershoot towards the

end which is reached after approximately 24 seconds (Heeger & Ress, 2002). During analysis, the BOLD response is modelled via the canonical haemodynamic response function (HRF) which consists of two gamma functions, explaining both the peak and the undershoot (Henson & Friston, 2006). Noteworthy is the fact that the BOLD response is much slower than the underlying neuronal activity. The indirect recording of neuronal activity via neurovascular coupling causes fMRI to have a relatively poor temporal resolution. Further, the magnitude of the BOLD response is very small (only ~2 % signal change in the visual cortex to e.g. a light flash) which limits statistical power.

Recording fMRI: When recording brain activity by means of fMRI, the brain (also referred to as a volume) is divided into horizontal slices which are acquired sequentially in a time-frame of a few seconds. The researcher can decide between descending, ascending, and interleaved recordings, regarding the order in which the slices are recorded. One also has to decide on the number of slices and their thickness. Each slice can further be subdivided into 3D data units, so-called voxels. The size of these units also has to be decided upon by the researcher and strongly depends on the size of the regions of interest and further on the time, the scanning of the whole volume should maximally take, the repetition time (TR).

2.2 fMRI data preprocessing

Having recorded fMRI data, several processing steps have to be carried out in order to prepare the data for later statistical analysis. After the rejection of the first few images (to allow for saturation effects), these comprise both temporal and spatial aspects; more specifically slice-time correction (correction for differences in slice acquisition time), realignment (rigid body motion correction), unwarping (optional; accounting for susceptibility by movement interactions), normalisation (global and local adjustments to a template), and smoothing (blurring of the data) all of which will be described in more detail in the following.

Slice-timing: As slices are acquired sequentially, activity measured in different slices represents different points in time. Statistical analysis on the other hand assumes that the whole volume (e.g. brain) is collected at one time point. In order to obtain slices representing the same moment, slices have to be shifted in time. In order to do so, one has to identify a reference slice (fixing it as time point 0) according to which all other slices are shifted: slices recorded earlier have to be shifted to a later point in time while later slices have to be brought forward. As a result, all slices will have the approximate value that they would have had, had they been acquired at the same time. This alignment is done through interpolations which can also lead to errors in calculation. This is especially the case for distant slices. Therefore, one should pick a slice as a reference slice that is closest to the region(s) of interest.

Realignment: During recording fMRI data, one cannot prevent all (head-) movements of the volunteers within the scanner. These movements however corrupt the data and thus have to be accounted for before further analysis. During the realignment process, all acquired images are put into the same position/orientation without changing the images of the brain itself ("rigid-body transformation"). This is done for both rotations and translations in all three dimensions (x, y, z). In order to do so, one has to pick an image as a reference image (usually the first image of the first session) to which all following images are aligned. Calculated realignment parameters can later be introduced into statistical analyses as separate regressors in order to account for movement related effects, i.e. to extract confounding movement related "activations" from stimulus-elicited activations.

Unwarp: Unwarping can be combined with realignment in one processing step. In addition to realignment, unwarp accounts for movement by susceptibility interactions and is especially useful when stimulus-related movements are present in the data.

Normalisation: Each individual brain differs in size and shape when compared to others. One is however mostly interested in making comparisons between individuals or

groups and relating the findings to reported results in literature. In order to be able to do so, one thus has to normalise each individual brain to a standard brain, the template. The matching between template and individual brain is done using 12 linear parameters in a global way, i.e. affecting the brain as a whole in a linear fashion: rotation, translation, resizing, and shearing, all of which are applied in all three dimensions (x, y, z). In a subsequent step, non-linear transformations are applied. This way, local changes are induced to minimize differences between the individual and the template brain and brains become more comparable regarding anatomical details.

Smoothing: Despite the normalisation, there will still be small differences between individual data sets, regarding interindividual anatomical alignment. In order to minimize these, one can blur the data by smoothing it prior to statistical analysis. Smoothing involves a convolution procedure: every voxel is multiplied with the weighted average (Gaussian kernel) of its surroundings. This way, voxels in the closest neighbourhood are taken into account more so than far away ones, i.e. have stronger weights than others. In order to smooth one has to decide on the size of the smoothing kernel, the so called FWHM (full width at half maximum), which influences how many neighbouring voxels are taken into account. Choosing the size of this kernel is not trivial as several aspects are affected by it. On the one hand one wants smoothed data to still show the structures one is interested in, on the other hand, one is interested in gaining similar data over individuals. For instance, if one is interested in smaller structures, such as the amygdala, one should pick a smoothing kernel that approximates the size of it whereas one can pick a bigger kernel if one is interested in the occipital cortex, a much bigger structure. It also makes a difference whether one is interested in individual or group data: for individual data a smaller smoothing kernel can be used than for group data as the latter include several individual data that can still differ. In addition to the aforementioned aspects, there are yet other aspects why smoothing is a helpful tool during preprocessing: Smoothing leads to an increased signal to noise ratio (SNR) by removing

noise, which mostly manifests in high spatial frequencies. This is possible as BOLD responses are usually expressed in lower spatial frequencies. It further helps to make the data normally distributed and to satisfy the Gaussian Field Theorem's application requirements to correct for multiple comparisons in statistical analyses.

Together, these preprocessing steps help to improve data quality and enable one to carry out the analyses planned to answer the study aims.

2.3 fMRI data analysis

Having preprocessed the data, one can turn to the analysis. Most analyses consist of two steps. In the first step (single subject level or first level), individual data are analysed. In the second step, the already analysed single subject data are pooled and group analyses can be computed. I will briefly describe the procedures of these analyses in the following.

Single subject level: Statistical analyses are carried out using the general linear model (GLM) approach. In the GLM, the time series of each voxel are analysed separately; the analysis of fMRI data is thus 'univariate' (Frackowiak, Friston, Frith, Dolan, & Mazziotta, 2007). First of all, a model has to be specified that predicts the observed data. The underlying formula is as follows: $Y = X * \beta + \varepsilon$; with as many $X * \beta$ as conditions. In other words, the GLM is an equation expressing the observed data (Y) in terms of a linear combination of weighted (parameter β) explanatory variables (X) and an error term (ε; Frackowiak et al., 2007). In order to specify a model, one has to indicate how many sessions and which conditions existed in the experiment and what kind of events occurred. Each condition that one wants to investigate has to be modelled as a separate regressor, thus resulting in as many regressors as conditions included in the design. Each *event* within this condition then has to be modelled as a stick function, containing ones at the times of stimulus presentation and zeroes otherwise, convolved with a canonical HR function, as implemented in Statistical Parametric

Mapping (SPM; Wellcome Department of Imaging Neuroscience, London, UK). The latter step is introduced as delayed (indirect) haemodynamic responses are measured. Taking all regressors together with a session constant term, one gets the so-called design matrix that one uses to explain the data. In the design matrix, further factors, such as behavioural ratings or movement parameters can be included as regressors in order to account for additional factors that explain additional variance. In a last step, data and design matrix are high-pass filtered as slow drifts have to be removed and a correction for temporal autocorrelations is carried out.

The now specified model with all its regressors and session constant terms then has to be estimated. Parameters (β) are estimated in order to minimize the difference between the data (Y) and the predicted responses, resulting in as many so-called beta-images as there are regressors. As this procedure is carried out for each voxel, there are now regression coefficients (β) for all voxels, indicating how strongly a certain condition influenced activity within each voxel. Subsequently, statistics can be calculated. In order to do so, one first has to specify so-called *contrasts* through which one compares e.g. one condition or 1st level with another by using t-tests or F-tests. This is done by introducing contrast weight vectors. If one had for instance four conditions, like in the present work happy, angry, neutral, and fearful items that constitute one regressor each, and if one was further interested in a greater response to angry items when compared to neutral items, one has to apply the following contrast weight vector: [0 1 -1 0]. Zeroes lead to an exclusion of the respective condition from that comparison. The results of this procedure are so-called contrast images that reflect the difference between two or more conditions, i.e. a weighted combination of beta images. Now, images are ready for possible statistical analysis (e.g. t-tests), even on the first level. Images now represent summary measures of individual responses to certain stimulation categories or comparisons. If one is however interested in group comparisons, one has to raise the contrast images to the second level, as a summary measure of each individual.

Group level: As indicated above, contrast (or beta) images of all participants that one wants to include in group analysis have to be used as input for further analyses. Now, the design matrix includes as many ones as there are participants that should be included, as only one image per person is present. One is interested in the mean response over all participants. This can further be compared to another group by comparing the means (over all participants) of the two groups. In order to do so, one can for example calculate t-tests (e.g. two-sample t-test or paired t-test), analysis of variance, or multiple regressions. In SPM, a correction for non-sphericity of the error term is implemented, correcting for dependencies or unequal variance. This is important as parametric tests assume that statistical models include errors that are distributed spherically. Having estimated the model on the second level, one can now test the significance of the observed effects by linear contrasts at a specified threshold. The end results of statistical analyses are statistical maps (t- or F-values) showing voxels that are significantly activated given a certain threshold. Through overlaying this map onto a structural image one can now identify areas involved in the task used. It is important to bear in mind that separate tests are carried out for each voxel. To ensure a correct use of statistical analysis, one now has to correct for the multiple tests carried out. This is usually done by using a correction based on the theory of "Gaussian random fields" (GRF; Worsley, Evans, Marrett, & Neelin, 1992) that corrects for independent resolution elements (so-called resels), i.e. groups of voxels - because one cannot assume that each voxel represents an independent measure. There are also other alternative corrections, such as the "Bonferroni Correction" that corrects for all the tests carried out (dividing the probability threshold by the number of tests; more conservative than GRF in most cases) and the "False Discovery Rate" (FDR; slightly more liberal). Concerning these corrections, one can choose whether one is interested in correcting activations over the whole brain (i.e. many thousands of voxels) or rather specific brain areas (a more manageable number of voxels; also called "small volume correction"). The latter should only be used if one has a clear enough hypothesis regarding specific

structures, the regions of interest (ROI). Preferably, a standard mask should be used rather than a sphere around an activation peak.

2.4 Dynamic causal modelling

While the traditional approach of SPM is grounded in the concept of functional segregation, it is becoming increasingly clear that a complete picture of brain function needs to also include the concept of functional integration. Several approaches exist for investigating connectivity of fMRI data, such as correlating the BOLD time-series of different regions. However, such types of analysis (functional connectivity, i.e. temporal correlations between remote regions) have important drawbacks, as connectivity is measured on the haemodynamic level and lacks directional information. A recently established technique that addresses both challenges is dynamic causal modeling (DCM; Friston, Harrison, & Penny, 2003), which allows investigations of effective connectivity (i.e. the influence that one neural system exerts over another; Friston, 1994) at the neuronal level. DCM is a generic approach for inferring unobserved neural states from measured brain activity. Based on a bilinear model of neural population dynamics that is combined with a haemodynamic forward model, three sets of parameters are estimated: (I) parameters mediating the influence of extrinsic inputs on the states (i.e. direct influence of a stimulus on regional activity), (II) parameters mediating intrinsic coupling among the states (i.e. inter-regional influence in the absence of experimental modulations), and (III) parameters allowing the inputs to modulate that coupling (i.e. change in the connectivity between regions induced by experimental procedures). For the present work, only parameters (I) and (II) will be relevant.

Model specification: In the first step, models one wants to test and compare have to be constructed. These consist of a number of regions that are connected intrinsically in specific ways: forward, backward, bidirectional, or unconnected. Further, an input region has to be

identified. In order to estimate DCMs, time-series have to be extracted from all regions included in the models first.

Time series extraction: DCM rests on fMRI time-series extracted from activation peaks in different regions. At this stage, special care has to be taken in selecting appropriate coordinates where time-series are extracted from: they have to lie within the identified areas (anatomical and functional constrains) and further – if interested in group comparisons - the choice of coordinates should be unbiased, i.e. not favouring one group. If one chose coordinates from a region in which only one group shows significant activations this is likely to bias the estimates of effective connectivity to and from that region. Having chosen the models one wants to compare, having further extracted the time-series from the specified coordinates, and having estimated these models, one can compare the models.

Inference on model space (Bayesian model selection): In order to identify the most likely model, random effects Bayesian model selection (BMS) can be used as implemented in SPM (Stephan, Penny, Daunizeau, Moran, & Friston, 2009). In this phase, the model that fits the data best but is least complex at the same time specified is identified among all models, i.e. the identified model represents an ideal balance between accuracy and complexity. This is desirable in order to avoid overfitting and to allow generalization (Pitt & Myung, 2002). The results of the inference on model space using BMS are reported using the exceedance probability φ_k. φ_k represents the probability that a specific model (k) is more likely than any of the other models contained in model space. The exceedance probability φ sums to one over all models (model space) included in the BMS procedure.

Inference on model parameters: Having identified the optimal model in each group via random effects Bayesian model selection, one can test parameter estimates (i.e. the strength) of input and intrinsic connections of the 'winning' model for significance, using a random effects approach (Stephan et al., 2010). This is done for each group separately. In a

subsequent step, group differences can also be tested, by using e.g. two-sample t-tests on the parameter(s) of interest. As one carries out more than one test, one now has to correct for the number of tests carried out, e.g. by using Bonferroni correction, although this correction for multiple comparisons is rather conservative in the presence of dependencies among the parameters.

2.5 Psycho-physiological interaction

The psycho-physiological interaction, in short PPI, is another approach to investigate effective connectivity (Friston et al., 1997). A PPI aims at finding a correlation in the activity profile of two brain regions that differs depending on the context, such as experimental conditions. Underlying is the idea that two interacting brain regions will not only show a correlation of activity levels over time (indicating a functional association between them), but that these interactions may be further modulated depending on psychological contexts, thereby changing the correlation found between these regions. Using a PPI analysis, one is thus interested in brain regions whose activity time-courses show a higher correlation with the extracted activity time-course of a specific seed region under a specific experimental condition when compared to another. Note that the influence of the specific context is very important, as brain regions may show unspecific correlations in activity levels over time, independently of the experimental conditions, as for example regions receiving the same sensory input can theoretically do.

On the first level, the design matrix of each individual consists of three regressors: 1) the time course of activity within a seed region, 2) the psychological variable (a stimulus regressor, created by subtracting one stimulus regressor from another), and 3) their product. Only the interaction term (the third regressor, i.e. the product of the time course regressor and the stimulus regressor) is then raised to the second level, where population inference regarding condition-dependent coupling between two brain regions can be made. This

analysis thus highlights brain regions in which the third regressor (interaction term) is a good description of activity, i.e. those in which the seed region's time course has a stronger effect under a specific experimental condition when compared to another. Although not used in the analyses reported here, group comparisons can also be computed, testing for differences in this coupling between groups. Note however, that as the PPI is based on correlative computations, information on directionality cannot be obtained using this method – other methods or previous knowledge have to be called upon.

3 Study 1: Validation of auditory stimuli

3.1 Introduction

In order to be able to stimulate participants with emotional sounds, validated datasets with emotional prosody stimuli were inspected for possible later use. These existing and available stimulus sets comprised whole sentences (e.g. “Database of German Emotional Speech”; see http://database.syntheticspeech.de) or single words (as for example the “Affective Norms for English Words” (ANEW); see http://csea.phhp.ufl.edu/media/anewmessage.html) voiced in different emotional tones, or vocal non-speech sounds, such as sighs or laughs (for example the “Montreal Affective Voices” or the “International Affective Digitized Sounds” (IADS); more information on both sets can be found at http://vnl.psy.gla.ac.uk/resources_main.php and http://csea.phhp.ufl.edu/media/iadsmessage.html, respectively). For the present work, however, purely emotional signals (speech stimuli) that were free of any semantics and similar in their phonetic structure were needed in order to carry out both phoneme and emotion discrimination tasks. Thus, a new data set had to be created.

Within our extended group, auditory stimulus material existed in auditory recording streams that needed to be pre-processed, i.e. cut into single stimuli, equalized as to loudness (in order to avoid confounding loudness effects), rated as to its usefulness, and later validated. In the following section I will describe these steps, the selection, and the validation of the stimulus material (study 1) for studies 2 to 4.

3.2 Methods

Preprocessing of the stimuli: The stimulus material consisted of recorded auditory streams spoken by ten female (five of which were young) and ten male actors (again, five old and five young). Twenty different bisyllabic pseudo words (‘baba‘, ‘babu‘, ‘dede‘, ‘dedu‘, ‘fafa‘, ‘fafi‘, ‘gigi‘, ‘gigo‘, ‘lolo‘, ‘lolu‘, ‘none‘, ‘nono‘, ‘rara‘, ‘raro‘, ‘sasa‘, ‘sasu‘, ‘tete‘,

‘teti‘, ‘wowe‘, ‘wowo‘) were voiced in five different emotional tones each (fearful, neutral, happy, sad, and angry). Each word and emotional tone was repeated at least three times, resulting in a total of more than 6000 stimuli. Stimuli had bee recorded continuously and therefore had to be cut. In order to gain stimulus material that was as authentic (i.e. natural) as possible, stimuli were cut at 30 ms pre-onset and 50 ms post-offset, so that rise and fall in amplitude were present, just like in normal situations. Stimuli were further normalized with respect to mean sound pressure level (80dB) in order to avoid loudness effects that could account for later effects found in behavioural and functional imaging data. This was done, knowing that a central characteristic of emotional speech, loudness (Banse & Scherer, 1996; Kappas et al., 1991; Scherer, 1981; Scherer, 1986), was being removed, possibly making it more difficult for participants to identify such items.

Validation of the stimulus material: I pre-selected 632 acoustic stimuli through auditory inspection from this stimulus set, while ignoring the gender of the speaker, the emotional category or syllables as some words were more authentic in specific emotions than others. Further, some actors were especially good at miming a particular emotion but again not all of them. Thus, a controlled selection of pseudo-words, emotions, and actors was unfortunately not possible. All selected stimuli seemed to be the most convincing items representing the five emotional categories happiness, sadness, anger, fearful, and neutral.

Participants: 32 participants (18 female) took part in this study. None of the volunteers had any neurological problems or history of psychological illness. Two female participants were not able to finish rating all items due to illness and their ratings were thus removed from later analyses. Thus, 30 participants (16 female; age mean ± sem. = 26 ± 0.74) completed the whole experiment. Participants were instructed as to the purpose of the study and were asked to proceed at their own pace in order to gain a high-quality validated stimulus set (see

Appendix 2 for the original instruction sheet in German). All participants had normal or corrected to normal vision and normal hearing, as evidenced by self-report.

Procedure: Participants came in maximally fours, all doing the task at the same time in one experimental room, in front of one PC each. Movable walls separated participants and thus ensured an undisturbed completion of the task. For each volunteer the volume was adjusted individually to guarantee for optimal intelligibility. The pre-selected 632 stimuli were presented via headphones. For each stimulus, participants had to fill in ratings on a graphical user interface (Figure 2), regarding the gender of the speaker (female or male), the pleasantness of the stimulus [i.e. the mix of the word itself with the emotional tone and the voice of the speaker; from absolutely unpleasant (= 0) over neutral (= 5) to absolutely pleasant (= 10)], and the arousal level [again ranging from not arousing at all (= 0) over neutral (= 5) to absolutely arousing (= 10)]. Participants did not see any numerical values for the sliders but only the slider position itself (i.e. visual analogue scale).

Participants had to judge the emotional tone-category in two different ways, both via forced-choice and by rating the intensity of each emotion on a slider; from not at all (= 0) to absolutely (= 10). Sliders for all eight different kinds of emotions were put up as possible alternatives, with only five emotions actually being presented (fearful, happy, neutral, sad, and angry; additional rating possibilities were disgust, surprise, and pain). The later were included in order to create a pure recognition task rather than a discrimination task as the discrimination of emotions has proven to be much easier than the recognition of emotional valences (Banse & Scherer, 1996). Participants were ignorant of this. The slider-option was included in the rating process in order to be able to differentiate the “pureness” of emotional tone, i.e. to identify stimuli clearly belonging to one emotional category based a more differentiated measure than the forced-choice option. Slider positions were randomized at the beginning of each trial regarding their starting position in order not to bias later responses.

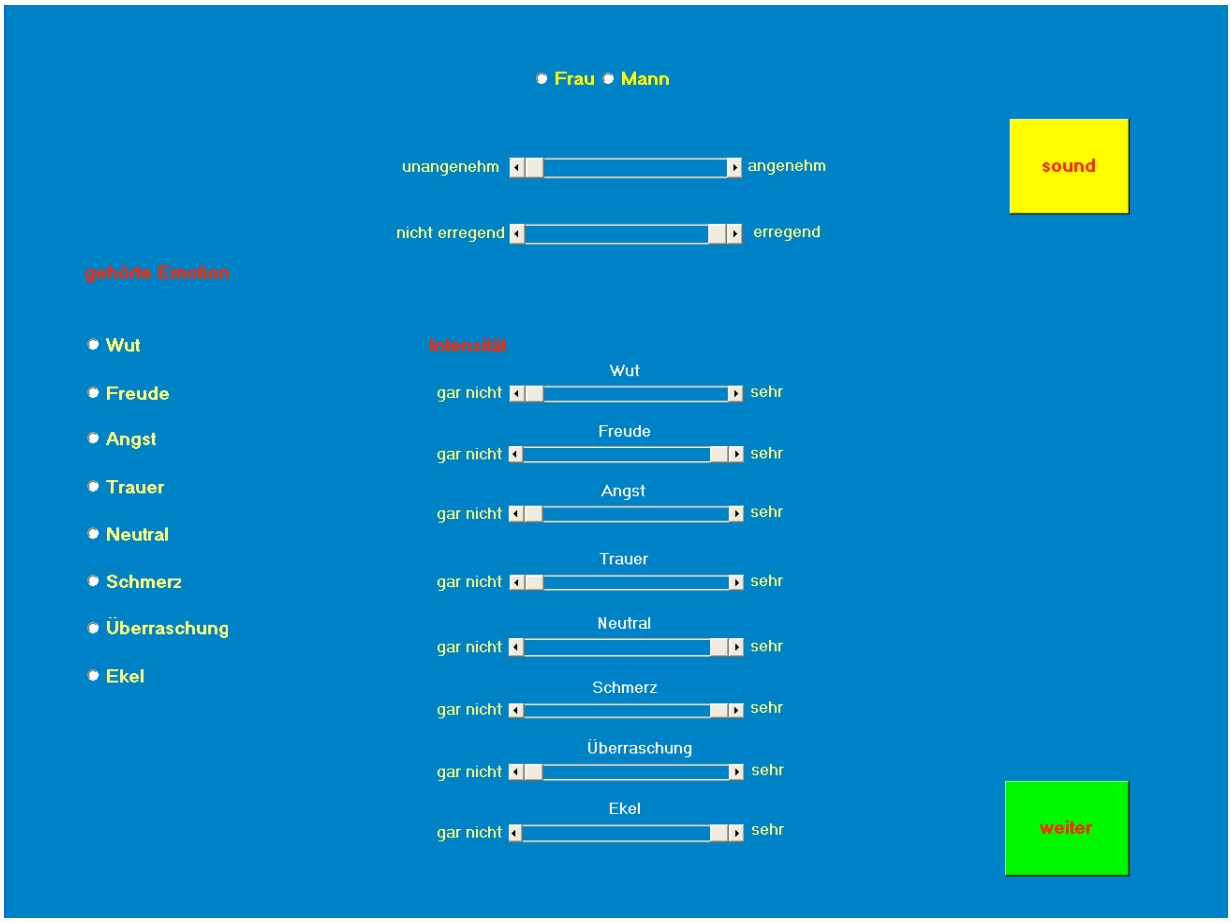

Figure 2. Graphical user interface which participants used for the validation of the stimulus material in study 1. Visual analogue scales were present as well as forced-choice options.

Participants completed blocks of 125-130 stimuli each at their own pace. They were able to listen to the stimuli as many times as they pleased and as was necessary. The order of the stimuli was randomized within each block and the blocks were randomized across participants. No more than two stimuli of the same emotional category were presented consecutively in order to control for context effects. Each block contained a roughly equal amount of stimuli from all five different emotional categories. On average, participants took ~6 ¼ hours to complete the ratings for all stimuli. All volunteers came back several times and were remunerated when having finished rating all stimuli. This delayed payment was introduced to increase the participants' compliance.

Analysis of the stimuli: For the selection of the final validated stimulus set, several criteria had to be met. In order to obtain optimal stimuli, only items that received (a) more than 80% in the intensity ratings of the respective emotional category in (b) the correctly recognized emotional category (i.e. in the correct forced choice rating option) were kept for further consideration. Amongst these chosen stimuli, only the 30 best (regarding pureness and intensity) of an emotional category were considered under further aspects. For the imaging experiment, a subset of those stimuli was selected based on a) their availability in both female and male voices and b) whether they were suitable to serve as a target in both the vowel and the emotional task.

In short, all stimuli selected had to meet the following criteria:

- correctly recognized emotional category in the forced-choice section,
- more than 80% intensity rating in the respective emotional category (slider),
- available in both a female and a male voice,
- usable for both an emotion and a vowel discrimination task, thus:
    - available in all emotional categories (fearful, happy, neutral, and angry),
    - while also available in all vowel catergories (a, e, i, and o).

3.3 Results

As a result, the following pseudo words were included into the main experiment: ‘baba’, ’babu’, ’dede’, ’tete’, ’gigo’, ’gigi’, ’lolo’, and ’wowo’. Each of these items was spoken by both a female and a male actor in a fearful, happy, neutral, and an angry voice, resulting in a total of 64 different pseudo words (16 stimuli per emotional category and per vowel category) for the main experiment. Sadness as a fifth emotion was excluded from the final data set as it would have presented a negatively biased stimulus-set (valence-wise). Also, sad items often

gained relatively high ratings on the 'pain' and 'fear' rating scales which was not desired as these ratings identified them as too heterogeneous -regarding the emotional category - for a clear categorization. Stimuli belonging to the final data set should be easily identifiable as belonging to one specific emotional category. See Tables A2a-d in the Appendix 3 for all chosen stimuli, including their average ratings for each emotional category separately. Average length of all chosen 16 stimuli in each category were (mean±sd) 871±170ms, 732±140 ms, 631±110 ms, and 676±90 ms for neutral, happy, fearful, and angry items, respectively. Except for neutral items which were significantly longer ($F_{(1,3)}$=10.01; p<.001), stimuli did not differ statistically in duration over emotional categories. The fact that neutral items were longer than others is however not surprising as one aspect of emotional prosody is that the speech rate changes (Banse & Scherer, 1996).

3.4 Summary of findings

The validation study aimed at creating a stimulus set usable in two different task contexts, namely emotion discrimination and vowel discrimination. In study 1, this data set was extracted from recording streams of many syllables spoken in different emotional tones by both young and old female and male actors. The extracted final data set now consisted of 16 stimuli per emotional (angry, fearful, neutral, and happy) and vowel (a, e, i, and o) condition that were easily recognizable and thus usable for the studies ahead.

4 Study 2: Emotional auditory processing in the blind

4.1 Introduction

Emotional signals are of major relevance in social interactions and strongly involve the amygdala, a core structure in affective processing that receives input from all sensory modalities (LeDoux, 2007; McDonald, 1998). In human social interactions the visual and auditory modality are the most important input channels regarding emotional content. Neuroimaging studies have established a consistent relationship between visual emotional processing and amygdala activation (Gläscher et al., 2004; Hariri et al., 2002; Morris et al., 1996; Reinders et al., 2006; for meta-analyses on this topic see Costafreda et al., 2008; Phan et al., 2002), whereas results in the auditory domain are less clear (Buchanan et al., 2000; Costafreda et al., 2008; Fecteau et al., 2007; Grandjean et al., 2005; Schirmer et al., 2008). Similarly, lesion studies have led to mixed results concerning auditory emotion processing following amygdala damage (Adolphs & Tranel, 1999; Adolphs et al., 2005; Scott et al., 1997).

Recent studies could furthermore show that the amygdala is modulated by experimental manipulations, such as attention and task salience (Hsu & Pessoa, 2007), current goals (Cunningham, Van Bavel, & Johnsen, 2008), and contextual demands (Ousdal et al., 2008). Further, there is accumulating evidence for an amygdala involvement in the processing of novelty and ambiguity (Whalen, 2007; Wright & Liu, 2006; Zaretsky, Mendelsohn, Mintz, & Hendler, 2010), unpredictability and uncertainty (Herry et al., 2007; Hsu, Bhatt, Adolphs, Tranel, & Camerer, 2005), and social cognitive and interactive processes (Adolphs, 2003; Kennedy, Gläscher, Tyszka, & Adolphs, 2009), supporting a more generalized function of the amygdala than just emotional processing. Taking a broader perspective, it has been proposed that the amygdala may play a pivotal role in detecting behaviourally relevant content

(Adolphs, Tranel, & Damasio, 1998; Sander et al., 2003; Todd, Evans, Morris, Lewis, & Taylor, 2010 among others; see chapter 1), thereby allowing for efficient orienting of processing resources towards salient events. This form of relevance detection could also explain the amygdala's habituation to repetitive stimulation; e.g. Breiter et al. (1996), Mutschler et al. (2010): As stimulation with the same or a similar item is repeated, the informational content becomes smaller and smaller and accordingly, amygdala activation decreases. Most recently, Todd & Anderson (2009) suggested that the amygdala might be regarded as a hub of different networks mediating both rapid and extended responses to diverse events of emotional salience.

Conceptually, the detection of salient information should predominantly rely on the sensory modality that provides the most reliable information in social interactions to guarantee for highly efficient detection of relevant events. Collignon et al. (2008) could show that participants preferentially categorised the affective expression based on the visual modality in incongruent situations, thus demonstrating a visual dominance in emotional processing. This pattern of results changed however when the visual stimulation became less reliable under the same incongruent conditions. In the latter situation, participants favoured relying on auditory information. The authors could thus show that the perception of emotions is not rigidly dominated by visual input but rather more flexible and appropriate for a given situation and the reliability of the present modality channels.

Yet, no one would argue that in most sighted humans, vision is the most trained and dominant sensory modality for a large number of functions (Hartcher-O'Brien, Gallace, Krings, Koppen, & Spence, 2008; Posner, Nissen, & Klein, 1976). Among these, the affective state of others is assessed with high precision from facial cues. In agreement with this notion, the amygdala is known to be reliably involved in the processing of emotional visual, in particular facial information (e.g. Gläscher et al., 2004; Hariri et al., 2002; Morris et al., 1996;

Reinders, den Boer, & Büchel, 2005; for meta-analyses see Costafreda et al., 2008; Phan et al., 2002). Accordingly, less consistent results regarding the amygdala's involvement in auditory emotion processing could be related to the less well developed proficiency in recognizing emotions from acoustic signals. Thus, in sighted, the amygdala might be superiorly tuned to the detection of emotional social signals in the visual domain, because vision provides the individual with the most reliable information and thus presents the dominant sensory modality. Consequently, if vision is compromised, this should then be accompanied by a change in allegiance of the amygdala. The amygdala should now predominantly serve another sensory modality that is optimal for sensing the emotional state of others.

However, an alternative account of amygdala mediated auditory emotional processing also exists which is based on the necessity of visual experience. The possible necessity of visual experience for brain's development and function has been tested recently in a number of studies, addressing different cognitive and sensory phenomena, such as the mirror neuron system (involving a premotor-temporoparietal network; Ricciardi et al., 2009), tactile working memory (involving the dorsal cortical pathway; Bonino et al., 2008), category specificity for animate and inanimate objects (involving ventral visual cortex; Mahon, Anzellotti, Schwarzbach, Zampini, & Caramazza, 2009; Pietrini et al., 2004), and the percept of tactile flow (involving area hMT+; Ricciardi et al., 2007). Consensus of all these studies was that visual experience is not crucial for the brain's development. It is however currently unclear whether this also applies to the amygdala which constitutes a central part of the brain's emotional system. In an extreme view one could even speculate that amygdala responses to auditory emotional stimuli might simply be explained by visual imagery of the matching emotional faces to the voices presented within an experiment. Thus, maybe the stimulus material in some studies seemed more authentic and illustrative and therefore led to amygdala activations (Bach et al., 2008; Fecteau et al., 2007; Johnstone et al., 2006; Morris et al., 1999;

Phillips et al., 1998; Sander & Scheich, 2001; Sander et al., 2005; Schirmer et al., 2008) while it did not elsewhere (Bach et al., 2008; Buchanan et al., 2000; Ethofer, Anders, Wiethoff, et al., 2006; Grandjean et al., 2005; Jäncke et al., 2001; Mitchell et al., 2003). This view however seems rather speculative and rather far-fetched.

In order to clarify these two issues (the effect of dominance and expertise on the amygdala and the possible necessity of vision), I chose connatally blind people as one sample for my work. Connatally blind people (from now on only called blind) represent an ideal population as they have to rely on non-visual cues in order to efficiently interact with others and are thus more trained in audition on the one hand. On the other hand, they have never experienced vision hence also excluding the possibility of visual experience and visual imagery of an emotional face as an explanation for amygdala activations.

As described previously, blind individuals outperform sighted peers in diverse tasks and modalities. These performance advantages have frequently been paralleled by additional activations of the occipital cortex (e.g. Sadato et al., 1996; Weeks et al., 2000). So far however, auditory processing of emotions and its implementation in the amygdala have not been investigated in blind individuals yet.

I therefore presented blind and sighted matched volunteers with auditory emotional stimuli in an fMRI paradigm, allowing me to test (a) if visual experience is needed for the amygdala to process acoustic emotional stimuli – assuming that it is not, as the amygdala represents an old and evolutionary important structure and (b) whether amygdala activation is influenced by the higher proficiency of the blind in recognizing auditory emotional signals, which belong to their dominant sensory modality in social interactions – assuming that expertise may indeed play an important role.

4.2 Hypotheses

I expected to find the following effects in blind and sighted:

- Blind individuals outperform sighted controls in auditory tasks, as evidenced by:
    - Shorter reaction times (RT) and higher accuracy rates in the blind than in the sighted in the vowel discrimination task.
    - Shorter RTs and higher accuracy rates in the blind than in sighted controls in the emotion discrimination task.
- The augmented behavioural performance of blind individuals goes in hand with increased additional activations of the occipital cortex.
- Greater emotion-specific amygdala activation in the blind than in the sighted (excluding the necessity of visual experience for amygdala function and also excluding visual imagery as possible reasons).
- Increased amygdala activation in the blind is correlated with behavioural performance in the blind (indicating that it is not blindness per se that drives amygdala activations but rather expertise).
- Stronger intensity ratings for emotional stimuli in the blind (based on the greater relevance and a more differentiated perception of blind individuals).
- Blind and sighted participants do not differ personality-wise, as evidenced by a lack of differences in personality questionnaires (excluding the possibility that underlying personality trait could account for differences in amygdala activation).

4.3 Methods

Participants: 22 volunteers took part in the study. Eleven connatally blind volunteers (five males), were matched with sighted participants according to gender, age, and approximate

educational level (see Appendix 1 for details). Handedness was assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). One blind participant had to be excluded from the analyses because of psychotropic medication, so her matched control was also excluded, resulting in two matched groups of ten individuals each [blind: age (mean±sem): 35±3; sighted: age (mean±sem): 35±3]. Participants were remunerated for participation. All participants were equally familiar with the scanning situation as it was the second time for each participant to enter an fMRI scanner. This was important in order to ensure that the scanning situation itself would not be perceived as frightening. Volunteers did not suffer from any affective disorders, were not taking any psychotropic medication, and had no history of neurological or psychiatric disease, apart from blindness. All participants had normal hearing. The acoustic volume level was adjusted individually to ensure optimal comprehension. The average loudness did not differ significantly between the two groups ($mean \pm sem_{(blind)}$= 81.10±0.62; $mean \pm sem_{(sighted)}$= 81.45±0.77; $t_{(18)}$=0.34, p=0.74). Participants gave written informed consent and were remunerated for their participation. The study was approved by the local ethics committee.

Stimuli: The newly developed and validated acoustic stimulus data set from study 1 was used. Stimuli were eight different meaningless bisyllabic pseudo-words (baba, babu, dede, tete, gigo, gigi, lolo, wowo) spoken by both female and male professional actors in an angry, happy, neutral, or fearful voice, resulting in a total of 64 different stimuli. In order to avoid habituation effects, stimuli with the same emotional tone were equally distributed throughout the experiment with a maximum of two similar events (same emotion and/or vowel) in successive trials.

Procedure: In this study, participants went through different experimental phases. The first step involved an instruction as to fMRI and the experiment itself. All information forms and fMRI questions were read by healthy participants but were read out to blind participants.

All participants further talked to me and a medical doctor about their answers in the questionnaires and possible further medical issues or questions. Having read the information sheets, signed the consent forms, and being approved for experimental purposes by a medical doctor, participants had to fill in several personality questionnaires regarding social desirability, trait anxiety, emotional regulation, and affectiveness. These were introduced in order to be able to exclude differences in underlying personality traits between blind and sighted participants which might account for the effects observed in fMRI activations. Participants completed the German versions of the 'Social Desirability Scale' (SDS; Crowne & Marlowe, 1960; Lueck & Timaeus, 1969), the 'State-Trait Anxiety Inventory' (STAI, trait part only; Laux, Glanzmann, Schaffner, & Spielberger, 1981; Spielberger, Gorsuch, & Lushene, 1970), the 'Cognitive Emotion Regulation Questionnaire' (CERQshort; Garnefski, Kraaij, & Spinhoven, 2002; Garnefski & Kraaij, 2006), and the 'Positive and Negative Affect Schedule' (PANAS; Krohne, Egloff, Kohlmann, & Tausch, 1996; Watson, Clark, & Tellegen, 1988). I read out all questions and possible answers to both blind and sighted participants in order to guarantee for comparable situations in both groups. The underlying ideas and constructs of each questionnaire are described in Appendix 4. See Appendix 5 for the German general instructions sheet.

Following this experimental part, every participant went through a training session to ensure a good comprehension of the tasks, timing demands, and finger-response assignment (index- and middle finger of both hands). The two tasks practiced during this stage involved a) the discrimination of the emotional tone (happy, angry, neutral, and fearful) of a voiced semantic-free auditory stimulus (32 words; 8 from each category), and b) the discrimination of the first vowel (a, e, i, and o). Each trial consisted of a short acoustic warning cue (550 Hz, 100 ms) followed by the bisyllabic stimulus (300 ms after cue onset). Participants were asked to respond as quickly and as accurately as possible. Average trial duration was 5.5 seconds (range 4-7 s), including a jittered inter trial interval of 0-3 s. Acoustic feedback was given

only in the practice session. Stimuli during training were different from stimuli used in the MR session to avoid possible habituation effects in the amygdala caused by repeated exposure of emotional stimuli (Breiter et al., 1996; Fischer et al., 2003). All participants were blindfolded, so that the training phase and the main experiment were as similar as possible. It was important for participants to get used to this situation, as in the MR scanner, all of them had to be blindfolded to guarantee for identical sensory input conditions in the two groups.

In the fMRI experiment both tasks were completed in two consecutive sessions. Participants were asked to give their responses, using individual buttons on a MRI-compatible response pad, each corresponding to one possible answer (a, e, i, and o or happy, fearful, neutral, and angry), as learned during training. Stimuli were presented over MR-compatible electrodynamic headphones (MR ConFon, Magdeburg, Germany). Volunteers were equipped with two custom-made MR-compatible response pads, one for each hand and completed the same tasks as during training but this time did not get any feedback. One session consisted of 128 trials (16 different new stimuli per emotion or first vowel; each presented twice). The order of the two tasks was randomized across participants with matched participants receiving the identical order of trials, tasks, and finger-response key assignment.

For this study, I chose an event-related design, i.e. stimuli from different emotional or vowel categories are presented within the same session (as opposed to blocked designs, where only stimuli of the same category are presented within the same scanning block) because block designs contain the danger of habituation and especially a sensitive structure as the amygdala will respond less and less (Breiter et al., 1996; Fischer et al., 2003). I included jittered intertrial intervals in order to a) decrease the predictability of each stimulus and b) increase the statistical power by increasing the variability in the signal.

After scanning, participants were asked to rate the stimuli presented in the experiment on several scales, similar to the ones used in study 1. Participants were presented with all

stimuli and had to rate each stimulus according to the gender of the speaker (female, male, not identifiable), the emotion(s) heard (again, all eight different options were presented: fearful, happy, neutral, sad, and angry, disgust, surprise, and pain), pleasantness, and also perceived threat. This time however, as opposed to study 1, I played each stimulus to the participants and told them the possible answers. This change was introduced as both groups should be treated the same way. Participants had to indicate numerical values for their answers (0-10), apart from the forced-choice option and gender questions. I played each stimulus as many times as the volunteer needed to hear it. Due to technical problems, data of two participants were unfortunately lost (one from each group).

fMRI data acquisition: fMRI data were acquired on a 3 Tesla system (TRIO, Siemens, Erlangen, Germany), equipped with a 12 channel head coil. 40 transversal slices (slice thickness: 2 mm; 1mm gap) were acquired in each volume (TR: 2.38 s; TE: 25 ms; flip angle: 90°; field of view: 208 x 208; matrix: 104 x 104); GRAPPA with PAT factor 2 and 48 reference lines) using gradient echo T2*-weighted EPI. Before analysis, the first five volumes of each participant were discarded to eliminate T1 saturation effects. High-resolution (1 x 1 x $1mm^3$ voxel size) T1-weighted images were acquired for each subject, using a magnetization prepared rapid gradient echo (MPRAGE) sequence.

fMRI data preprocessing: fMRI data processing and statistical analyses were carried out using statistical parametric mapping (SPM5; Wellcome Department of Imaging Neuroscience, London, UK). Data preprocessing comprised slice timing (correction for differences in slice acquisition time), realignment (rigid body motion correction), spatial normalization to a standard EPI template (including re-sampling at a resolution of 2x2x2 mm^3), and smoothing using an 8 mm (full width at half-maximum) isotropic Gaussian kernel. Data were also subjected to high-pass filtering (cutoff period, 128 s) and correction for temporal autocorrelations (based on a first order autoregressive model).

fMRI data analysis: Statistical analyses were carried out using a general linear model approach. On the first level, each event type (fear, happiness, neutral, and anger) was modelled as a separate regressor, thus resulting in four regressors. Each event was modelled as a stick function convolved with a canonical hemodynamic response function as implemented in SPM5. After model estimation, the following contrasts were computed for each participant: all stimuli (including happy, neutral, angry, and fearful stimuli), anger>neutral, fear>neutral, and happiness>neutral. Contrast images from each subject were raised to the second level. Within-group effects were analysed using one-sample t-tests for: anger>neutral, fear>neutral, and happiness>neutral. For group comparison (blind versus sighted), two-sample t-tests (including non-sphericity correction for possible unequal variances of the error term in the two groups) were used. The following contrasts were used: blind (emotion>neutral) > sighted (emotion>neutral) for each emotional condition as well as the inverse contrasts. As there were no statistical differences in amygdala and occipital cortex activation between the emotion and vowel discrimination tasks and as no group x task interactions were found in RT data, functional data from both tasks were collapsed. To investigate the relationship between behaviour and BOLD responses within the amygdala during the emotion discrimination task, the average individual reaction time was included as a covariate on the second level. Because of strong hypotheses regarding BOLD responses in the amygdala and the occipital cortex, the search volume was limited to these regions and activations are reported at a threshold of $p<0.05$ (corrected for multiple comparisons via GRF, if not stated otherwise). Correction for the amygdala was based on the amygdala mask (threshold 40 %) of the Harvard-Oxford subcortical atlas as provided by FSL (FMRIB Software Library). Correction for the occipital cortex was based on a search volume of a 40 mm diameter sphere centred anatomically in the midline of the occipital lobe at 0, -84, 12 mm.

4.4 Results

Based on previous findings, I expected to find overall augmented auditory capabilities in the blind, indexed by better behavioural performance. As hypothesized, blind volunteers were significantly faster than the sighted in both tasks (main effect of group: $F_{(1,18)}$=14.2, p=0.0014), indicating superior acoustic discrimination abilities. This difference was paralleled by significantly greater activation of the occipital cortex in the blind than in the sighted in response to acoustic stimuli (peak x, y, z in mm: 20, -92, 30; $t_{(18)}$=8.34, p<0.002, corrected). This activation extended into the dorsal and ventral visual stream and was independent of the emotional content of the stimuli and the task employed (Figure 3; see Figure A1 in Appendix 6 for averaged parameter estimates across the occipital cortex and Table A3 in Appendix 7 for coordinates). In an additional whole-brain analysis an activation of the right superior occipital cortex (20, -92, 30; $t_{(18)}$=8.34, p<0.020, corrected) and of the right middle occipital cortex (32, -92, 10; $t_{(18)}$=7.73, p<0.026, corrected) was observed.

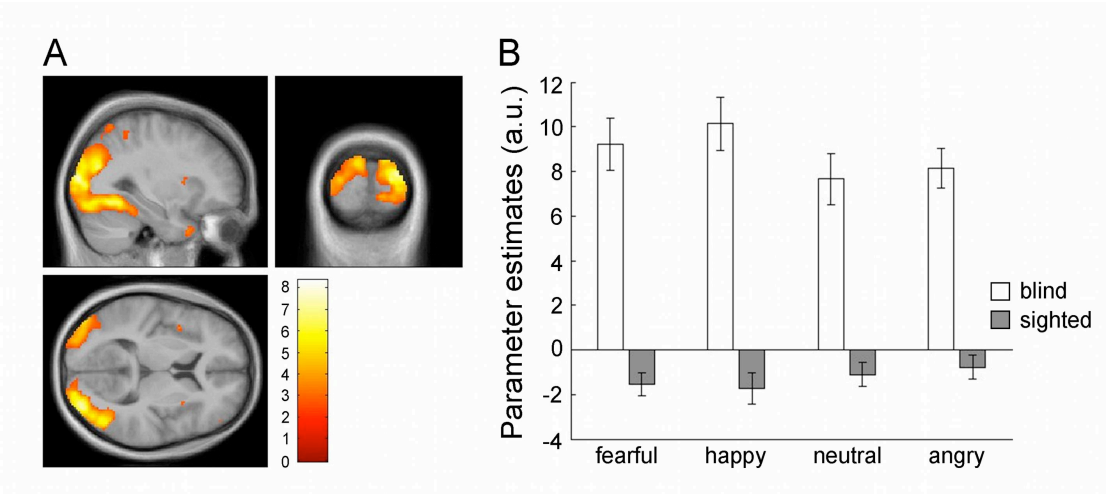

Figure 3. Activation pattern in the occipital cortex paralleling superior behavioural performance in the blind when processing acoustic stimuli, regardless of the emotional category and task. **A**) Stronger occipital BOLD (blood oxygen level dependent) signal changes in the blind compared to sighted controls following acoustic stimulation; visualization threshold at p<0.01. **B**) Parameter estimates (at 20, -92, 30 mm) for each individual emotion show a strong activation when comparing the blind with the sighted group. (* see References for permission of reproduction)

Apart from an advantage in the vowel discrimination task ($F_{(1,18)}$=12.22, p<0.003; Figure A2 in Appendix 8), the blind showed faster emotion discrimination as compared to the sighted controls ($F_{(1,18)}$= 7.05, p=0.016; Figure 4). This behavioural advantage differed across different emotions and was smaller for happy items, leading to a significant group (blind vs. sighted) by condition (emotional category) interaction ($F_{(3,54)}$= 3.44, p=0.023). Happy items were the most difficult items to recognize which is in agreement with previous findings, indicating that happiness is more difficult than other emotions to identify in vocal stimuli (Elfenbein & Ambady, 2002).

Additional behavioural data are depicted in Tables A4 and A5 in Appendix 9 and 10 for reaction times and accuracy data respectively. For both sets, 3-way repeated-measures ANOVAs were calculated with the factors group (blind, sighted), task (EMO, VOC), and emotion (fearful, happiness, neutral, and anger). Further, ANOVAS were computed for each task separately, comparing behavioural data of all emotional conditions.

Regarding the idea that the amygdala serves the sensory modality that is most reliable and in which participants have the highest expertise, I predicted stronger amygdala activation in the blind than in the sighted in response to acoustic emotional stimulation. Indeed, superior processing of fearful and angry (but not happy items) in the blind was paralleled by greater amygdala activation when compared to the sighted group.

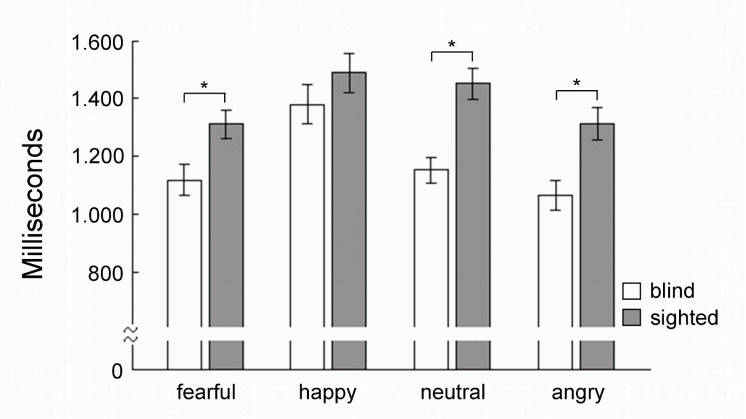

Figure 4. Mean reaction times for stimuli from all four emotional conditions of both blind and sighted volunteers in the emotion discrimination task. Reaction times were recorded from stimulus onset onwards. Blind participants were significantly faster than sighted controls in all conditions, except for happy items.

A stronger BOLD signal change for fearful as compared to neutral stimuli in the right amygdala was observed in the blind (18, -8, -14; $t_{(18)}$=4.50; p=0.007, corrected). A homologous activation in the left amygdala did not survive correction for multiple comparison (-18, -6, -12; $t_{(18)}$=2.78; p=0.119, corrected). No significant activation was observed in the sighted group. Most importantly, comparing amygdala activation between the two groups to fearful vs. neutral stimuli (i.e. group by condition interaction) revealed significantly greater signal changes in the right amygdala in the blind (18, -8, -14; $t_{(18)}$=3.50; p=0.039, corrected; Figure 5A).

In response to angry stimuli compared to neutral stimuli, we observed a significant bilateral signal change in the amygdala in the blind (18, -6, -14; $t_{(18)}$=4.60; p=0.006, corrected and -18, -6, -12; $t_{(18)}$=3.67; p=0.028, corrected). A significant activation of the left amygdala was also observed in the sighted (-18, -10, -12; $t_{(18)}$=3.88; p=0.020, corrected). Importantly, when comparing both groups, there was again a significantly stronger activation in the right amygdala (18, -2, -16; $t_{(18)}$=4.58; p=0.007, corrected) in the blind than in the sighted (Figure 5B). No significant BOLD responses were found for happy items compared to neutral ones in either group (all p>0.19). In order to investigate the effect of expertise on the amygdala activation, RT data from the emotion recognition task was included in an additional independent analysis. This analysis revealed that reaction times to fearful stimuli in the emotion discrimination task showed a significant relationship with right amygdala activation in the blind (30, 4, -22; $t_{(16)}$= 3.71, p=0.045, corrected, Figure 5C). No significant relationship between reaction time and BOLD response in the amygdala was observed in the sighted group. Consequently, we observed a significantly stronger relationship in the blind than in the sighted (interaction: 30, 4, -22; $t_{(16)}$= 4.24, p=0.020, corrected). Even after excluding one extreme case we observed the same relationship in the amygdala of the blind (30, 4, -22; $t_{(15)}$= 4.43, p=0.018, corrected; see Figure A3 in Appendix 11) and a significantly stronger relationship in the blind than in the sighted (30, 4, -22; $t_{(15)}$= 4.93, p=0.009, corrected). All

other regression analyses using either performance to happy or angry items failed to reach significance.

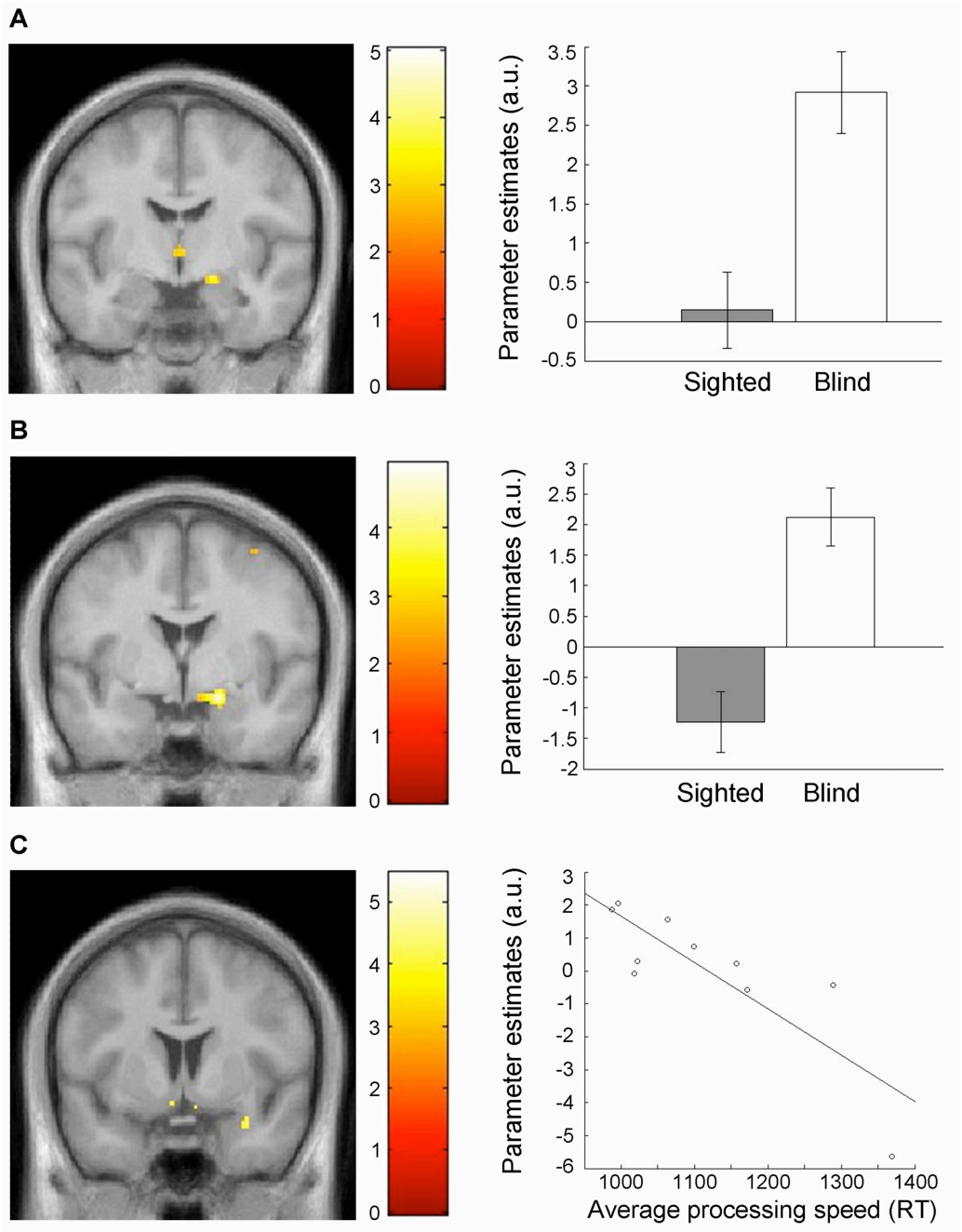

Figure 5. BOLD responses in the amygdala. The blind show stronger BOLD responses than the sighted in the right amygdala (group-emotion interaction effect) to **A**) fearful vs. neutral; at 18, -8, -14 mm and **B**) angry vs. neutral stimuli; at 18, -2, -16 mm; visualization threshold: $p<0.01$ (uncorrected). Bar plots show the parameter estimates at the peak voxel for blind and sighted volunteers (bars represent emotional category minus neutral; error bars represent standard errors of the mean). **C**) Relationship between the BOLD response in the amygdala in blind volunteers with their behavioural performance during the emotion discrimination task; at 30, 4, -22 mm visualized at $p<0.001$ (uncorrected). Shorter reaction times to fearful stimuli are associated with greater amygdala activation in the blind. In all images activation is overlaid on the mean structural image of all participants. (*see References for permission of reproduction)

In the post-scan validation phase, the blind rated each main (intended real emotion) emotion to be detected as significantly stronger/more intense than the sighted (fear: $t_{(16)}$=1.92, p=0.036; anger: $t_{(16)}$=2.92, p=0.048; happiness: $t_{(16)}$=2.86, p=0.010). Crucially, there was no significant difference for ratings of neutral stimuli between blind and sighted participants.

The analyses of the personality questionnaires provided evidence that the two groups did not differ significantly in any measured trait or personality scale, as shown in Figure 6. Neither the group difference of the SDS (p=0.85), nor the STAI-Trait (p=0.13) yielded statistical differences. Further the subscales of the CerqShort did not show any differences between the two groups: self-blame (p=0.83), acceptance (p=0.21), rumination (p=0.32), positive refocusing (p=0.26), refocus on planning (p=0.36), positive reappraisal (p=0.92), putting into perspective (p=0.54), catastrophizing (p=1.00), and other-blame (p=0.16). Finally, no group differences were found for either of the PANAS subscales: positive affect (p=0.30) and negative affect (p=0.53).

Possibly confounding effects such as differences in word length (see study 1) cannot account for the brain activations found in this study as the duration of happy, fearful and angry did not differ significantly while amygdala activation was only found for negatively valenced but not for happy stimuli. Further, differences between the two groups regarding emotional intensity ratings for the different emotional

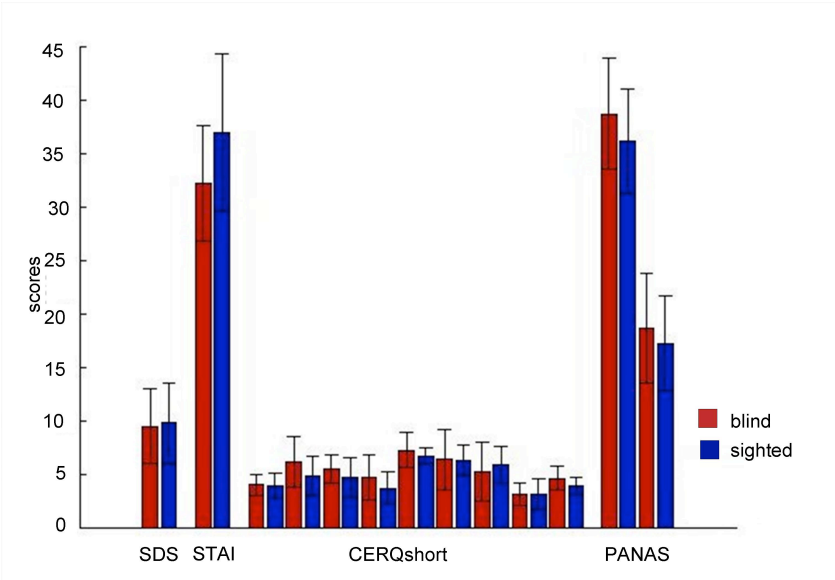

Figure 6. Blind and sighted participants gained similar scores in the four personality questionnaires.

categories cannot explain group differences in amygdala activation either, as the latter only differed for negatively valenced items while the first differed for all emotional categories, except for neutral items.

4.5 Summary of findings

As expected, I observed that blind participants indeed outperformed sighted matched controls in two different auditory discrimination tasks and that this performance advantage was paralleled by additional OCC activations in the blind, thus replicating and expanding previous findings. Further, I could show that visual experience is not necessary for the amygdala to respond to auditory emotional stimuli. Showing this, I can also exclude the possibility of visual imagery as a cause for amygdala activations. On the contrary, amygdala function was even increased in the blind, suggesting that the amygdala has indeed been affected by plasticity, now most likely subserving the most reliable modality for emotion detection. Furthermore, as there was a correlative relationship between fear emotion discrimination abilities and amygdala function, I was further able to provide evidence that it is not blindness per se that drives amygdala activation but rather the expertise the individual has gained in a certain modality: The better the behavioural performance, the greater the amygdala activation. Blind and sighted participants did not differ personality-wise which was important in order to exclude possible confounding effects of personality traits on amygdala function. Finally I could show that the increased perceptual abilities were also reflected in more differentiated perception and increased perceived emotional intensity of the stimuli.

5 Study 3: Connectivity of the occipital cortex in the blind

5.1 Introduction

Connatally blind individuals have never experienced vision and it is thus impossible for them to use visual imagery in different tasks. Nevertheless, activations of the visual cortex in blind individuals have frequently been reported in non-visual experiments (e.g. Amedi et al., 2003; Röder et al., 1999; Sadato et al., 1996). Over the last decade, these additional OCC activations were increasingly associated with cortical plasticity underlying the augmented behavioural performances of blind individuals in various different tasks. The recruitment of the visual cortex has thus been hypothesized to be essential for the blinds' exceptional abilities (Gougoux et al., 2005; Hamilton & Pascual-Leone, 1998; Röder et al., 1999). Associations were found between OCC activation and augmented performances in the blind (Gougoux et al., 2005) and several studies were able to provide direct experimental and clinical evidence for causal links between OCC recruitment and compensatory abilities in the blind.

Experimental evidence functional role of the OCC in the blind comes from a number of studies in which task performance of blind participants was impaired following transient disruption of OCC function, using transcranial magnetic stimulation (TMS). TMS pulses on the mid OCC induced increases in error rate and distorted somatosensory perception in the blind in a Braille reading task (Cohen et al., 1997). This disruptive effect of OCC-TMS was also found on Braille reading, reading speed, and repetition priming (Kupers et al., 2007). TMS applied to occipital regions was further shown to interfere with the performance of blind individuals in an auditory localisation task (Collignon et al., 2007; Collignon et al., 2009), verbal processing (Amedi et al., 2004), and the use of a sensory substitution device (visual-to-auditory) during object identification (Merabet et al., 2009). In sighted controls, no such impairments were found in either experiment.

Clinical support of such a causal link was provided by a case report (Hamilton et al., 2000) where a connatally blind woman became unable to read Braille after an ischemic stroke which caused bilateral damage to the OCC, while somatosensory perception was unaffected.

Thus, the functional relevance of OCC in the blind has been established for a number of aspects in both the tactile and the auditory modality. However, the pathways mediating non-visual information to the visual cortex are currently unclear. Recent data shed some light on tactile input into the visual cortex in the blind (Fujii, Tanabe, Kochiyama, & Sadato, 2009), but the route of auditory information flow to the blinds' visual cortex remains to be clarified, as modality-specific recruitment mechanisms most likely exist (Driver & Noesselt, 2008).

In 2002, Bavelier and Neville (also see Driver & Noesselt, 2008; Noppeney, 2007) suggested several possible, though not mutually exclusive, routes that could be transferring auditory information to the blinds' visual cortex: Plastic changes could be mediated through the reorganization of long-range subcortical connectivity (i.e. thalamo-cortical connectivity; A). This possibility however seems to be limited to developing organisms, relying on the stabilization of usually transient and redundant pathways (e.g. in the connatally blind mole rat where auditory stimuli reach the MGN and LGN via the inferior colliculus; Kudo, Moriya, & Mizuno, 1997; Rehkamper, Necker, & Nevo, 1994). Animal models show these changes to occur under evolutionary pressure (Kudo et al., 1997; Rehkamper et al., 1994), raising the possibility that they can also occur in connatally blind or deaf humans (e.g. Bronchti et al., 2002; Liu et al., 2007; but see Noppeney, Friston, Ashburner, Frackowiak, & Price, 2005; Shimony et al., 2006 who reported atrophied LGN in the blind). On the other hand, cortico-cortical connections between primary sensory cortices could be enhanced. These can be further subdivided into direct long-range cortico-cortical connections (B1) on the one hand (Bizley, Nodal, Bajo, Nelken, & King, 2007) and indirect cortico-cortical feedback

connections via intervening multimodal convergence zones (B2) on the other hand (Rockland & Ojima, 2003).

Tracing studies in animals provide structural evidence for all of these routes. Evidence for thalamo-cortical connections (A) has been reported in different species: in the mole rat (Bronchti et al., 2002), in adult natally enucleated opossums (Karlen, Kahn, & Krubitzer, 2006), and in enucleated rats Piche (2007). Larsen, Luu, Burns, & Krubitzer (2009) reported additional abnormal thalamo-cortical input in almost blind knock-out mice and Cappe, Morel, Barone, & Rouiller (2009) found multisensory interplay involving the thalamus in monkeys. These thalamo-cortical connections involved additional (i.e. re-routed) connections between usually disconnected regions. Evidence for direct long-range cortico-cortical connections (B1) in animals also comes from tracing studies. For instance Frost and Innocenti (1995) found cortico-cortical connections in immature cats and hamsters, respectively. Further, connections between A1 and V1 have been reported repeatedly: in ferrets (Bizley et al., 2007); monkeys (Cappe et al., 2009; Clavagnier, Falchier, & Kennedy, 2004; Falchier, Clavagnier, Barone, & Kennedy, 2002; Falchier et al., 2009); cats (Hall & Lomber, 2008), prairie voles (Campi, Bales, Grunewald, & Krubitzer, 2010), and in adult neonatally enucleated opossums (Karlen et al., 2006). Finally, Wang, Celebrini, Trotter, & Barone (2008) found electrophysiological evidence for multisensory convergence in early stages of cortical sensory processing, e.g. audio-visual convergence in V1. The authors assume that direct connections are probable. Evidence for indirect cortico-cortical feedback (B2) has also been reported in monkeys (Rockland & Ojima, 2003).

In humans, support for cortico-cortical connections comes from TMS and fMRI studies. When applied over S1, TMS increased OCC activity in early blind participants as evidenced by PET (Wittenberg, Werhahn, Wassermann, Herscovitch, & Cohen, 2004). When applied to dorsal extrastriate cortex of early blind volunteers, Collignon et al. (2007) found rTMS to

interfere with the use of a sensory substitution device and a spatial auditory localisation task. Also using TMS over OCC, Ptito et al. (2008) found sighted to experience phosphenes while blind participants reported tactile sensations. These findings were interpreted as resulting from strengthened cortico-cortical connections (via parietal VIP) rather than from thalamo-cortical coupling. Using resting-state fMRI, Eckert et al. (2008) found correlations between calcarine cortex and A1 in sighted participants. Further evidence for cortico-cortical connectivity from auditory and somatosensory cortex to visual cortex comes from activation-based fMRI studies in both sighted (den Ouden, Friston, Daw, McIntosh, & Stephan, 2009; Werner & Noppeney, 2010) and blind humans (Fujii et al., 2009), respectively. Calculating DCMs on fMRI data of blind and sighted volunteers, Fujii et al. (2009) reported indirect connections between S1 and V1 (via multimodal parietal areas) to have a better model fit than direct connections. Sparse support for thalamo-cortical connections in blind humans comes from a resting-state fMRI study (Liu et al., 2007). Note however, that a degeneration of the lateral geniculate nucleus (LGN) has also been reported in the blind (Noppeney et al., 2005; Shimony et al., 2006; but see Bridge, Cowey, Ragge, & Watkins, 2009). Hence, cortico-cortical connections seem more probable than thalamo-cortical connections to be mediating auditory responses in the visual cortex of the blind.

In order to investigate the underlying mechanisms of additional OCC activation in response to auditory stimulation in the blind, I re-analysed the functional imaging data set from study 2. This time, the effective connectivity (the influence one neural system exerts over another; Friston, 1994) between different cortical and thalamic candidate regions was of interest and thus dynamic causal modelling (DCM; Friston et al., 2003) was used. The brain areas (and their connections) I was interested in comprised the medial geniculate nucleus, the primary auditory cortex, and the primary visual cortex. The aim was to clarify whether thalamo-cortical or cortico-cortical connections drive the additional activations found in the OCC of the blind.

5.2 Hypotheses

I expected to find the following effects in blind and sighted:

- Auditory input into medial geniculate nucleus (MGN) should be equal in strength in blind and sighted participants.
- Connections between MGN and the primary auditory cortex (A1) should not differ between the two groups.
- Stronger connectivity should be evident between A1 and the primary visual cortex (V1) in the blind than in the sighted.
- Maybe, there are some difference in connectivity between the MGN and V1; if so, possibly greater in the blind than in the sighted.
- No enhancement of LGN-V1 connection in the blind compared to the sighted.

5.3 Methods

fMRI data preprocessing: In study 3, imaging data were preprocessed similar to study 2 and I will therefore only mention differences to study 2. Data were preprocessed using SPM8 (Wellcome Department of Imaging Neuroscience, London, UK). This time, realignment was carried out including the unwarp function (accounting for susceptibility by movement interactions) and the data were smoothed with a smaller (6 mm) isotropic Gaussian kernel. The latter change was introduced as I was interested in a structure smaller than the amygdala in study 2, namely the MGN (and the LGN).

fMRI data analysis: Statistical analyses were again carried out using a general linear model approach. This time, on the first level, all event types (fear, happiness, neutral, and anger) were pooled and modelled as one regressor. Again, each event was modelled as a stick function convolved with a canonical haemodynamic response function. Note however that the

two sessions were this time pooled into one session by concatenating the stimulus regressor, in order to facilitate DCM analyses. Two regressors that modelled each session mean were also included in the design matrix to compensate for possible session differences; another regressor modelled the transition between the two sessions. After model estimation, beta images (reflecting the stimulus regressor) from all participants were raised to the second level. At the second level, a two-sample t-test with non-sphericity correction (for possible unequal variance of the error term in the two groups) was carried out. Group specific contrasts and differential contrasts were computed (blind, sighted, blind > sighted, and sighted > blind), as well as a conjunction analysis across both groups [blind & sighted; based on the conjunction null hypothesis, testing for a logical AND (Nichols, Brett, Andersson, Wager, & Poline, 2005)]. An uncorrected threshold of $p < 0.005$ was used, but p-values for each peak that are corrected for multiple comparisons are also reported. Correction was based on cytoarchitectonic probability maps (included in the SPM anatomy toolbox as well as in FSL; Eickhoff et al., 2005) of the medial geniculate nucleus (MGN), the primary auditory cortex (A1), and the primary visual cortex (V1). In a control analysis the MGN was substituted with the lateral geniculate nucleus (LGN). Maps of those regions were thresholded at 50% and are described in more detail in the following references (V1: Amunts, Malikovic, Mohlberg, Schormann, & Zilles, 2000; A1: Morosan et al., 2001; MGN & LGN: Burgel et al., 2006). In all of the following analyses I will only address BOLD responses in these regions; no whole-brain analyses were carried out as I was only interested in specific brain areas. The underlying processing steps of DCM are described in chapter 1. Here, I will only give information as to the specific choices and settings involved in this analysis.

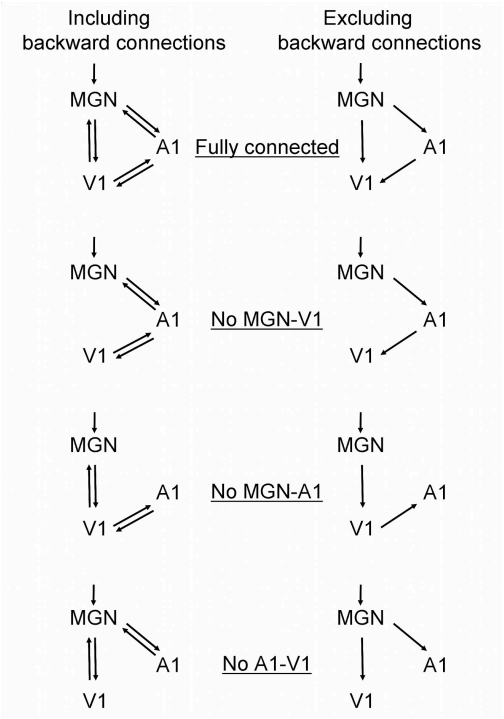

Figure 7. Schematic representation of the eight candidate dynamic causal models that were tested in this study. In all models the driving input was on the medial geniculate nucleus (MGN), which was connected to the primary auditory cortex (A1) and the primary visual cortex (V1). The models were specified separately for each hemisphere and only differ in their intrinsic connections.

Model specification: Eight different models consisting of three regions each (MGN, A1, and V1) were constructed in each participant for the left and right hemisphere separately (Figure 7). The extrinsic input (auditory stimulation) entered the system through the MGN as it has been unequivocally established that the MGN presents the major input site for auditory information to A1 (Hudspeth AJ, 2000). The constructed models thus only differed in the intrinsic connections that were specified between the three regions: a) a 'fully connected model' with connections between all three regions, b) a model with no connection between MGN and V1, c) a model with no connection between MGN and A1, and d) a model with no connection between A1 and V1. Each of these models existed in two different versions: Once with bi-directional connections and once with forward connections only; forward meaning connections emanating from MGN (see Penny, Stephan, Mechelli, & Friston, 2004 for a more extensive discussion of forward and backward connections in the context of DCM). As transmission of auditory information could also happen via rewired inputs from the inferior colliculus through the LGN in the blind (Bavelier & Neville, 2002), models including LGN instead of MGN were also constructed.

Time series extraction: DCM rests on fMRI time-series that were extracted from activation peaks in MGN, A1, and V1. Special care was taken in selecting only time-series from coordinates that were clearly located within the primary sensory cortices and the MGN

(and LGN), by using cytoarchitectonic maps of these three regions to constrain the search volume (see also below). Coordinates obtained from the random effects conjunction analysis were used as a starting point for time-series extraction. This ensured that not only similar anatomical loci in both groups were the basis of the DCM analysis, but significant responses were also present in blind and sighted at the identified location.

As local activation peaks differ across participants, individually adjusted coordinates for each participant were used for fMRI time-series extraction by employing a combination of functional and anatomical constraints in each of the three regions (MGN, A1, and V1). Per participant, the coordinates for fMRI time-series extraction were determined in each region by identifying the most significant activation peak that satisfied three conditions: a) it had to be significant at a level of $p<0.05$ uncorrected, b) it had to be within a sphere around the group peak of the conjunction analysis (4mm radius for MGN [and LGN]; 8mm radius for A1 and V1), and c) it had to be within the cytoarchitectonically defined mask. After identifying an individual peak, a sphere was placed around this peak (4mm radius for MGN [and LGN]; 8mm radius for A1 and V1) and the first eigenvector of the time series was extracted. Adjustment was also carried out in order to remove unspecific effects (session mean and session transitions).

If a participant did not show any significant BOLD responses in a region of interest (i.e. the intersection of sphere and mask), group coordinates of activation were used instead, because the sample size was rather small (10 blind and 10 sighted adults) and I could not afford to loose any further participants from analyses. Table A6 in Appendix 12 lists the coordinates of each peak from each participant and also indicates if a participant did not show significant responses in a search region. The substitution with group coordinates was necessary in only 11/120 cases - 120 being the sum of 20 subjects with three regions in each hemisphere. Note that this potential confound was controlled for as an additional analysis was

carried out in which only participants with significant responses were included. In two further control analyses (see results section for more details), simple within-group contrasts were used to identify second-level group peaks rather than the conjunction analysis.

Inference on model space (Bayesian model selection): Random effects Bayesian model selection (BMS) was used as implemented in SPM8 (Stephan et al., 2009). This procedure identifies the model that fits the data best amongst the whole set of models but is least complex at the same time. The results are reported using the exceedance probability φ_k, representing the probability that a specific model (k) is more likely than any of the other models contained in model space. In order to identify the best model out of all eight models described above, BMS was used for each hemisphere and group separately. Other authors have also performed model comparison on the site of input to the system (e.g. Ethofer, Anders, Erb, et al., 2006; Vaudano et al., 2009). In this work however, this was not done as it is unequivocally established that the MGN represents the major auditory input site to A1 (Hudspeth AJ, 2000).

Inference on model parameters: Having identified the optimal model in each group and hemisphere, the parameter estimates of both input and intrinsic connections of the winning model were tested for significance using a random effects approach (Stephan et al., 2010). Regarding group differences, only connections between MGN-V1 and A1-V1 were expected to differ, but the MGN-A1 connection and the input to MGN were also tested for possible group differences using two-sample t-tests. Bonferroni correction was used to correct the p-value for the number of tests within each parameter class (i.e. three tests, $p<0.017$ for intrinsic connections). As there should be stronger connections from A1 to V1 and possibly from MGN to V1 in the blind, one-tailed t-tests were used in these cases, but two-tailed t-tests otherwise. I will also report within-group results of input to MGN and all intrinsic connections using a one-sample t-test (two-tailed).

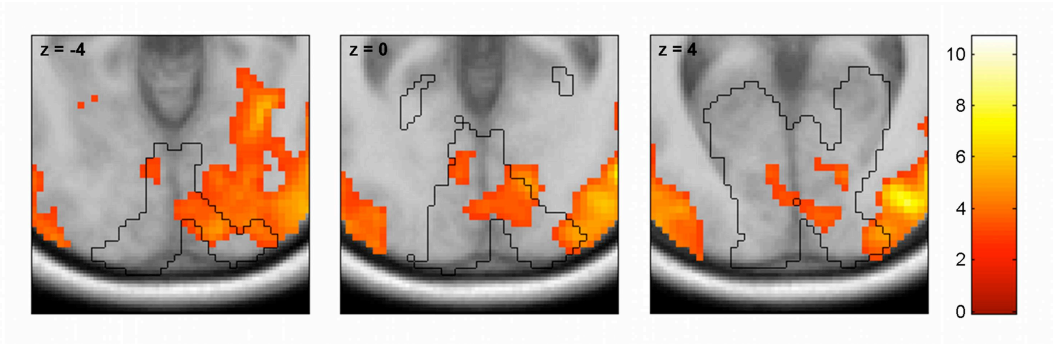

Figure 8. Group differences in primary visual cortex BOLD responses. The blind group showed significantly stronger BOLD responses in the primary visual cortex (V1) than the sighted group. The black outline represents the V1 mask used in this study (based on cytoarchitectonic probability mapping). The visualization threshold is set to $p<0.005$ uncorrected, and the activation maps are displayed on the average structural image of all participants (representative transversal slices at -4mm, 0mm, and 4mm). The colour bar indicates t-values.

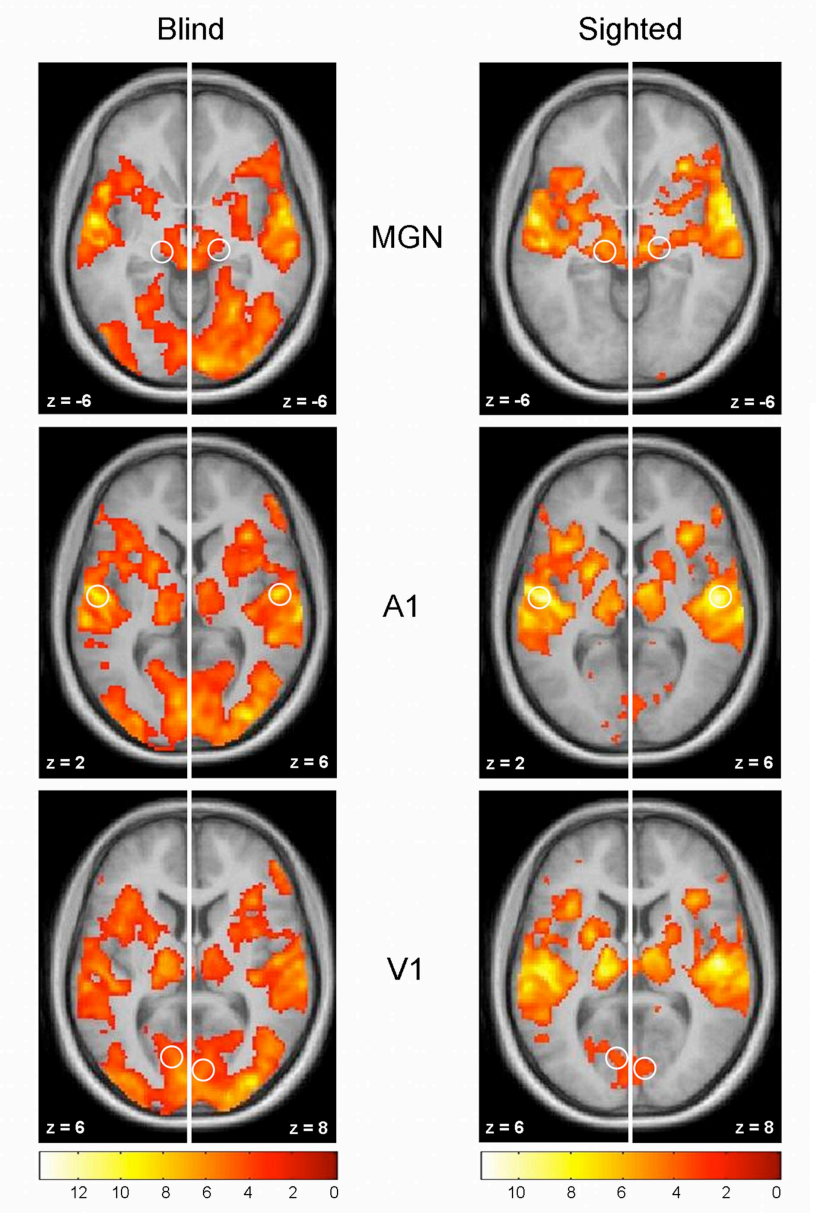

Figure 9. Activation maps depicting group-specific BOLD responses. The white circles indicate the locations (MGN, A1, V1) at which significant responses were detected in the conjunction analysis across groups. The visualization threshold is set to $p<0.005$ uncorrected, and the activation maps are displayed on the average structural image of all participants. The colour bars indicate t-values.

5.4 Results

MGN, A1, and V1: First I checked whether BOLD responses differed between the two groups in the regions of interest (MGN, A1, and V1). While the blind showed a significantly enhanced activation of BOLD response in bilateral V1 (Figure 8), this was not the case for the MGN and A1. The sighted on the other hand showed slightly increased activations within bilateral A1 (Table A7 in Appendix 13). In order to avoid any bias for subsequent DCM analyses, a conjunction analysis over both groups was used to obtain coordinates for later DCM analyses. This ensured that a) both groups showed significant responses at the identified peak and b) time-courses from identical regions entered the DCM analysis. Significant BOLD responses were found in all three regions in both hemispheres (Figure 9 and Table A8 in Appendix 14). At the identified voxels, these responses did not differ significantly between the two groups, not even when using a very liberal uncorrected statistical threshold of $p<0.05$.

In a next step, random effects Bayesian model selection (BMS) was used within each group and hemisphere in order to identify the optimal model to explain the data. I found the fully connected bidirectional model to clearly outperform all other models in both hemispheres of both groups (exceedance probability of $\varphi>0.85$ in all cases; Figure 10), suggesting that this low-level neuro-architecture is very much alike in both blind and sighted adults.

Having identified the fully connected model as the best model, input and connection strengths were tested for significance within each group (Figure 10, and Table A9 in Appendix 15). As expected, auditory input into MGN was highly significant in both groups and both hemispheres. Connections from MGN to A1 were positive and by far the strongest. Overall, backward connections were generally weaker than forward connections. In the sighted, several backward connections and the connection from the left A1 to left V1 failed to reach statistical significance.

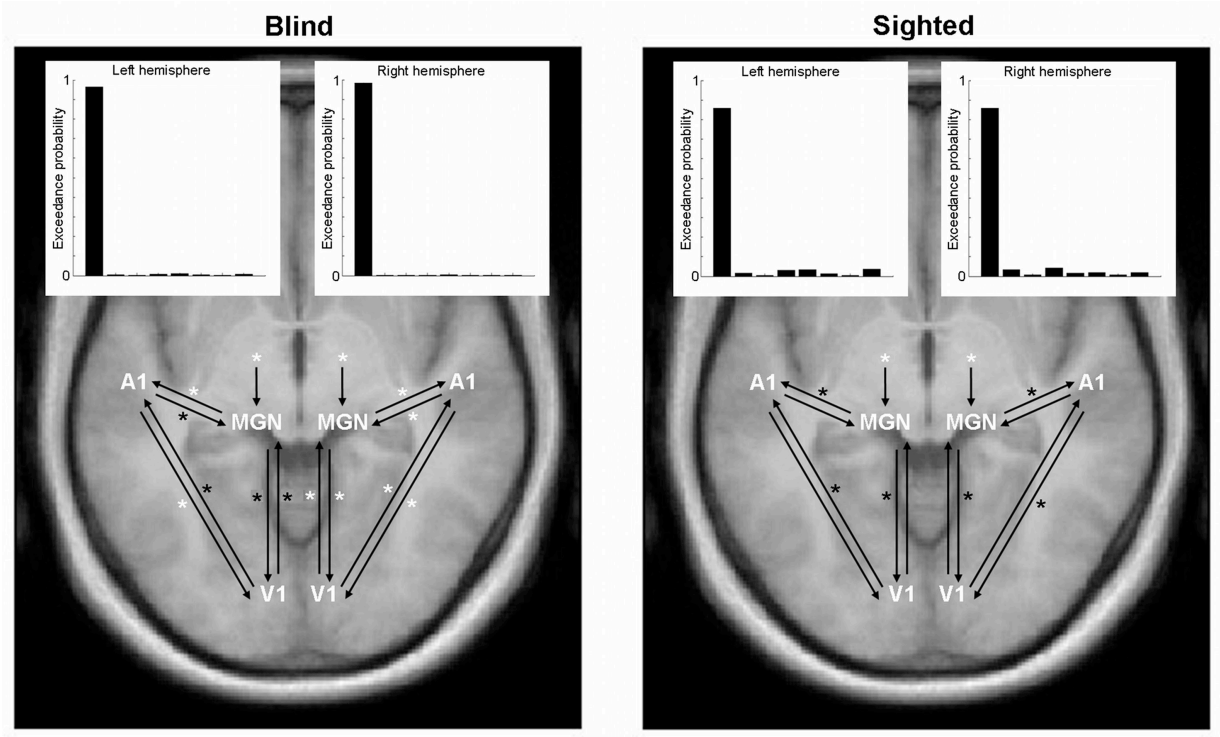

Figure 10. Model comparison results and parameter estimates of inputs and intrinsic connections for each group. White insets show the results of the random effects Bayesian model comparison procedure, with bars indicating the exceedance probability for each of the eight models shown in Figure 7. The winning model in both hemispheres and groups was the fully connected model (first bar). The within-group strength of the input and intrinsic connections of the winning model are represented by the asterisks in the lower part of the figure (black: $p<0.05$ uncorrected, white: $p<0.05$ corrected; two-tailed testing). The exact scores can be found in Table A8 in Appendix 15. The background image is a transversal slice of the average structural image of all participants (at z=-6mm, the location of the MGN peaks).

I next turned to testing group differences of model parameters. As hypothesized, no significant group differences were found for the input to MGN and the MGN-A1 connection (all $p>0.2$). As expected, A1-V1 connections were stronger in the blind than in the sighted (Figure 11) in both hemispheres (left: $t_{(18)}=2.48$, $p=0.012$; right: $t_{(18)}=3.23$, $p=0.002$); both survived the correction for multiple comparisons. Note that the effect of enhanced A1-V1 connectivity remained stable (though to a slightly lesser extent), when including only participants who showed significant BOLD responses within the search region in each ROI in the first-level analysis (Table A10 in Appendix 16 and Figure A4 in Appendix 17).

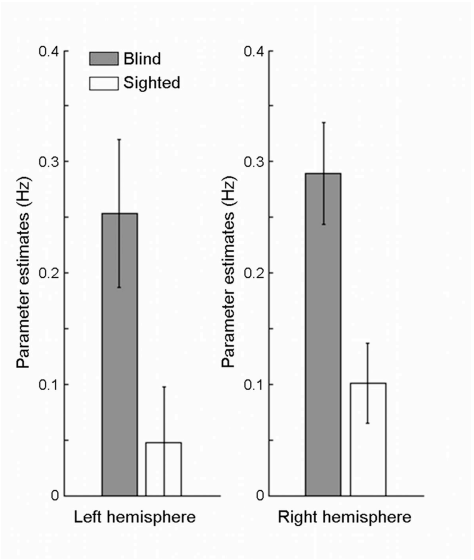

Figure 11. Connection from primary auditory cortex (A1) to primary visual cortex (V1). In both hemispheres the connection from A1 to V1 was significantly stronger in the blind group. This effect survived correction for multiple comparisons and was replicated in several control analyses.

Further, connections from MGN-V1 were slightly greater in the right hemisphere of the blind when compared to the sighted ($t_{(18)}$=1.16, p=0.057) but did not survive the correction for multiple comparisons. In the left hemisphere, no group differences were found, not even at an uncorrected threshold ($t_{(18)}$=-0.35, not significant; Figure 12 A).

LGN, A1, and V1: In another analysis, the MGN was substituted with the LGN, testing for the possibility of a rewired LGN in the blind, relaying auditory information to the primary visual cortex which has been reported in animals (Kudo et al., 1997; Sur, Garraghty, & Roe, 1988; Sur, Pallas, & Roe, 1990). BOLD responses in the LGN (obtained through the conjunction analysis) were weak and did not even survive an uncorrected threshold of p<0.005, let alone the correction for multiple comparisons [left: -22 -24 -6, $t_{(18)}$=2.00, p=0.03 (uncorrected), p=0.13 (corrected); right: 24 -24 -6, $t_{(18)}$=2.45, p=0.01 (uncorrected), p=0.07 (corrected)]. As expected, the connection from LGN to V1 was not enhanced in the blind when compared to the sighted but instead slightly (non-significantly) reduced (Figure 12b).

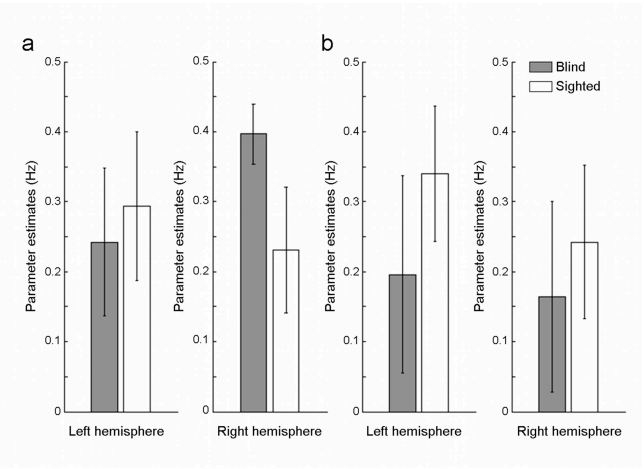

Figure 12. Connection from **A**) medial geniculate nucleus (MGN) and **B**) lateral geniculate nucleus (LGN) to primary visual cortex (V1). Note the non-significant reduction in connection strength from LGN to V1 in the blind.

Control analyses: The approach described above included identification of voxels in V1 based on the conjunction analysis, allowing for an unbiased selection of coordinates. This approach – which has also been taken by other investigators looking at group differences in connectivity (Fujii et al., 2009) – ensures that fMRI time-series from similar locations in both groups enter the DCM analysis. However, these regions are not necessarily the ones where maximal BOLD responses are observed in each group. Therefore, a complimentary control analysis was carried out, this time replacing conjunction peaks in V1 with group-specific activation peaks in V1 [blind group left hemisphere; -2 -88 4, $t_{(18)}$=7.48, p<0.001 (uncorrected), p=0.001 (corrected); blind group right hemisphere: 20 -100 10, $t_{(18)}$=8.89, p<0.001 (uncorrected), p<0.001 (corrected); sighted group left hemisphere: -6 -74 6, $t_{(18)}$=3.90, p=0.001 (uncorrected), p=0.160 (corrected); sighted group right hemisphere: 10 -66 14, $t_{(18)}$ =3.76, p=0.001 (uncorrected), p=0.254 (corrected)]. Again, BMS identified the fully connected bidirectional model in both hemispheres of each group (exceedance probability of φ>0.85 in all cases). Similarly, there was again a significant enhancement of the connection from A1 to V1 in both hemispheres in the blind (left: $t_{(18)}$=2.58, p=0.010; right: $t_{(18)}$=2.96, p=0.004), but no significant difference in the path from MGN to V1 (left: $t_{(18)}$=-0.40, n.s.; right: $t_{(18)}$=0.21, n.s.); no group differences were observed for the MGN-A1 connection and the input on MGN (all p>0.2).

In a last control analysis, all V1 voxels that were significantly activated in each participant's first-level analysis (p<0.05 uncorrected; note that every participant showed significant responses in bilateral V1) were included in the control analysis. While this analysis does not have any localizing power it represents a summary measure of each participant's BOLD responses within V1. Consistent with the above mentioned greater BOLD responses in the blind, the number of voxels that were significantly activated in each participant (i.e. the spatial extent of activation) was significantly higher in the blind than in the sighted in both hemispheres (left: $t_{(18)}$=4.34, p<0.001; right: $t_{(18)}$=3.32, p=0.002). Again, BMS clearly favored

the fully connected model (exceedance probability of φ>0.87 in all cases). The cortico-cortical connection from A1 to V1 was again enhanced in the blind in both hemispheres (left: $t_{(18)}$=2.09, p=0.026; right: $t_{(18)}$=2.91, p=0.005), although the effect was slightly smaller than in the other analyses and did not survive correction for multiple comparisons in the left hemisphere. No significant differences were observed in the connection from MGN to V1 (left: $t_{(18)}$=-0.21, n.s.; right: $t_{(18)}$=0.52, n.s.).

5.5 Summary of findings

As expected, the strength of auditory input into MGN did not differ between the two groups, indicating that the blind receive the same mount of sensory input. Thus, the starting point for auditory processing is the same in both groups. Following this processing step, information is transferred to A1. As with the input, the connection strength between MGN and A1 was not significantly different between the two groups. Coming to the crucial points, I hypothesized stronger connectivity between A1 and V1 in the blind. This was indeed the case, providing evidence that cortico-cortical connections mediate the additional activations of V1 in the blind. The remaining questions thus were: Are there also thalamo-cortical connections mediating this effect? And if so, are they mediated via the auditory MGN or rather rewired through the visual LGN? The analyses above showed clearly that - if involved - thalamo-cortical connections arising from the MGN do not (reliably) provide V1 with auditory information. Regarding the LGN, I can exclude it as a possible relay station for auditory information in blind humans. Hence, at least in blind humans, re-wiring does not seem to happen, fitting nicely to the described degeneration of the LGN in blind humans (Noppeney et al., 2005; Shimony et al., 2006).

6 Study 4: Deprivation or training-induced plasticity within the amygdala?

6.1 Introduction

In study 2, it was argued that the detection of relevant emotional information should predominantly rely on the most reliable sensory modality (Collignon et al., 2008; Klinge, Röder, & Büchel, 2010). Inconsistent results regarding amygdala involvement in auditory emotional processing could thus, in addition to methodical issues, be related to the less well-developed proficiency in recognizing auditorily transferred emotional cues in normally sighted humans. Therefore, connatally blind volunteers were matched sighted controls, showing superior behavioural performance in an emotion-discrimination task and increased amygdala activation to negatively valenced stimuli. The blinds' additional amygdala activation was further correlated with performance in the emotion discrimination task, suggesting that it may not only be blindness that modulates amygdala function in auditory emotional processing but also the proficiency one has gained in a sensory modality. However, one cannot unequivocally differentiate between plastic changes within the amygdala as an effect of blindness per se (i.e. deprivation-induced plasticity) or as an effect of training (i.e. use-dependent plasticity) as the sighted sample lacked any special auditory expertise.

Auditory expertise (proficiency as a result of training) can also be acquired by sighted people, profoundly improving behavioural performance. This has been demonstrated by studies with both non-musicians and musicians where specific trainings had an improving effect on behavioural performance in the auditory domain, such as pitch discrimination (Bosnyak, Eaton, & Roberts, 2004; Demany, 1985; Tervaniemi, Just, Koelsch, Widmann, & Schröger, 2005), micro-melody discrimination (Zarate, Delhommeau, Wood, & Zatorre, 2010), and auditory working memory (Gaab, Gaser, & Schlaug, 2006). Auditory training has also been shown to be accompanied by specific changes within the auditory cortex and

associated brain areas (after short-term training in non-musicians: (Bangert & Altenmüller, 2003; Bosnyak et al., 2004; Gaab et al., 2006); and long-term training in professional singers and musicians: (Elbert, Pantev, Wienbruch, Rockstroh, & Taub, 1995; Gaser & Schlaug, 2003; Lotze, Scheler, Tan, Braun, & Birbaumer, 2003; Pantev et al., 1998; Schneider et al., 2002; Shahin, Bosnyak, Trainor, & Roberts, 2003), which most likely mediate the behavioural improvements.

Professional actors represent another professional sample undergoing broad auditory trainings, with a special focus on auditorily transferred emotions. During classes on speech training – which constitutes a crucial part of the actors' education – actors focus on timbre, intonation accuracy, vowel quality, and sound intensity in the context of emotional expression. They do not only train these aspects, but – importantly – also receive auditory feedback, which allows for enhanced perceptual sensitivity to and greater control over auditory emotional expressions. Hence, actors have gained a high expertise in the auditory domain, especially when it comes to auditorily transferred emotions, and should thus be more proficient in this field than untrained sighted people.

I therefore invited professional actors and presented them with the same paradigm as previously employed in blind and sighted volunteers (study 2) to disentangle the two possible effects that might mediate enhanced behavioural performance and amygdala activations in the blind. If the effects we described previously were solely due to deprivation-induced plasticity, one would expect actors to show responses similar to untrained sighted controls (i.e. slower reaction times in the emotion discrimination task and weaker amygdala responses to negatively valenced auditory stimuli than blind volunteers). If, however, the previously described effects were mainly due to use-dependent plasticity, one would expect the actors to show enhanced responses compared to sighted controls (i.e. faster reaction times and stronger amygdala responses than sighted volunteers). Because of the previously observed correlation between behavioural performance and amygdala activity, suggesting that individual

proficiency is a pivotal mediating factor, I favoured the latter hypothesis. A further open question concerned the emotional intensity with which the stimuli would be perceived by the actors: previously blind volunteers gave higher emotional intensity ratings than sighted volunteers.

6.2 Hypotheses

I expected to find the following effects in the actor sample:

- Augmented behavioural performance compared to sighted controls due to auditory training (effects), as evidenced by:
    - Shorter reaction times in the emotion discrimination task.
    - Shorter reaction times in the vowel discrimination task.
    - Behavioural performance should be similar to that of blind individuals.
- Based on findings of a correlation between emotion discrimination performance and amygdala activation in the blind, hinting at training-induced plastic changes within the amygdala, I expected to find increased amygdala activation in actors compared to sighted controls.
- If there is an augmented activation level of amygdala in the actors, it should correlate with the behavioural emotion discrimination performance, as a further index of plastic changes due to proficiency within the amygdala.

I did not have any hypotheses regarding the ratings of the stimuli, nor did I expect to find big differences in the personality questionnaires.

6.3 Methods

Participants: Ten professional actors (5 males) took part in the present experiment. All actors were carefully matched with blind and sighted volunteers (studied in study 2) according to

age [actors: 35±8 (mean±SEM); the blind: 35±3; the sighted: 35±5], gender, and handedness (Oldfield, 1971). Note that sighted controls will be referred to as "sighted" and professional actors as "actors", despite the fact that actors are naturally also sighted. The participants neither took psychotropic medication, nor did they suffer from psychiatric or neurological diseases, as evidenced by self-report. Participants gave written informed consent and the study was approved by the local ethics committee. Before the completion of the task within the scanner, participants who had never been inside an MRI scanner were accustomed to the situation by explaining the MRI procedure to them and doing an "acclimatisation scan". During this scan, participants just laid inside the scanner, first with the scanner being off and then with the scanner being on. This was important in order to ensure that the scanning situation itself would not be perceived as frightening, which could also modulate amygdala responses.

Special care was taken in the selection of the actors. All participants included were professional actors, i.e. trained actors with at least 3 years in acting school, a drama diploma, later acting experience and currently working in theatres and films. In our sample, drama school was visited for 3 ¼ years on average (varying from 3 to 3 ½ years). As mentioned above, speech training and other auditory trainings constitute a crucial part of the actors' training and on average took up 4 ¾ hours of classes per week during drama school, not including homework. During these classes and their homework, actors are trained and receive feedback with regard to diverse aspects of their voice, such as emotional expression and transfer of emotional content, to name a few relevant examples. All except for one actor reported early beginnings of acting and singing experience, starting at the age of 15±4 years.

Stimuli and Procedure: In the present study, the same stimulus set and procedure were used as in study 2. The procedure consisted of the participants giving written informed consent, filling out the set of personality questionnaires (again, I read out all items and possible answers to the actors in order to create identical situations between actors, sighted

controls, and the blind), undergoing the training sessions for both the emotion discrimination and the vowel discrimination task, fMRI scanning during task execution, and the final rating of the stimuli. Here, actors who had never been inside an MR scanner underwent an "acclimatisation scan" - before the real MRI part - where they simply lay inside the scanner with the scanner switched off first and switched on later. As soon as they felt comfortable with the situation, the normal (f)MRI procedure started. This acclimatisation scan was introduced in order for the scanning situation itself not to be perceived as frightening as this could have big influences on amygdala activity.

fMRI data acquisition: The same scanning routine was applied as in study 2: fMRI data were acquired on a 3 Tesla system (TRIO, Siemens, Erlangen, Germany), equipped with a 12 channel head coil. 40 transversal slices (slice thickness: 2 mm; 1mm gap) were acquired in each volume (TR: 2.38 s; TE: 25 ms; flip angle: 90°; field of view: 208 x 208; matrix: 104 x 104); GRAPPA with PAT factor 2 and 48 reference lines) using gradient echo T2*-weighted EPI. Before analysis, the first five volumes of each participant were discarded to eliminate T1 saturation effects. High-resolution (1 x 1 x 1mm^3 voxel size) T1-weighted images were acquired for each subject, using a magnetization prepared rapid gradient echo (MPRAGE) sequence.

Behavioural data analysis. Reaction time and accuracy data of the emotion-discrimination task were analysed with STATISTICA (StatSoft. Inc.) using a two-factorial repeated measures analysis of variance (ANOVA, factors: group (3 levels: actors, blind, sighted controls) and condition (4 levels: fear, happiness, neutral, and anger). For comparisons without a-priori hypotheses (personality questionnaires and ratings), two-sided two-sample t-tests were calculated, using Matlab 7.5 (MathWorks Inc., Natick, MA, USA). Statistical differences at $p<0.05$ were considered significant. I will focus on reaction time and accuracy data from the emotion-discrimination task, as expertise effects in recognizing emotions and its driving effect on amygdala responses during auditory emotional stimulation

were of special interest. Note however, that actors - despite comparable accuracy levels - were also significantly faster in the vowel discrimination task than sighted controls, closely matching the blind's behaviour (see Figure A5 in Appendix 18).

fMRI data preprocessing: As in study 2, fMRI data processing and statistical analyses were carried out using statistical parametric mapping (SPM5; Wellcome Department of Imaging Neuroscience, London, UK). Data preprocessing comprised the correction for differences in slice acquisition time (slice timing), rigid body motion correction (realignment), spatial normalization to a standard EPI template (including re-sampling at a resolution of 2x2x2 mm^3), and smoothing using an 8 mm (full width at half-maximum) isotropic Gaussian kernel. Data were also subjected to high-pass filtering (cutoff period, 128 s) and correction for temporal autocorrelations (based on a first order autoregressive model).

fMRI data analysis: Statistical analyses were carried out using a general linear model approach. On the first level, each event type (fear, happiness, neutral, and anger) was modelled as a separate regressor, thus resulting in four regressors. Each event was modelled as a stick function convolved with a canonical hemodynamic response function as implemented in SPM5. After model estimation, the following contrasts were computed for each participant: anger>neutral, and fear>neutral. In a next step, contrast images from each participant were raised to the second (group) level. Two-sample t-tests (including non-sphericity correction for possible unequal variances of the error term in the two groups) were used to compare groups (blind versus actors and sighted versus actors) and always tested for a group-by-emotion interaction: e.g. blind (emotion>neutral) > actor (emotion>neutral) and vice versa for each emotional condition; note that this interaction can be implemented in a two-sample t-test as the contrast image of a difference (emotion > neutral) from each participant was raised to the second level. Following the previous approach from study 2, the functional data from both tasks was collapsed (since there was no significant group x task interaction in RT data (p=0.4)). Because of the hypothesis involving an increase of amygdala

activation, the search volume was limited to this region and activations at a threshold of $p<0.05$ (corrected for multiple comparisons, if not stated otherwise) based on the amygdala mask (thresholded at 40%) of the Harvard-Oxford subcortical atlas as provided by FSL (FMRIB Software Library) are reported. Note that only data in response to negatively valenced stimuli (fear and anger) were analyzed as these were the ones where blind and sighted controls differed in study 2.

In a post-hoc analysis motivated by unexpected behavioural and fMRI results, I tested whether the ACC does exert a negative influence on the amygdala during the processing of angry stimuli. To this end an effective connectivity approach, namely a psycho-physiological interaction analysis (PPI; Friston et al., 1997; see chapter 2 for more detailed information) was employed. The first-level design matrix of each participant consisted of three regressors: 1) the time course of the seed region, 2) the psychological variable (a stimulus regressor), and 3) their product. The time course of the ACC for each participant originated from the ACC peak coordinates obtained in the group analysis, and the psychological variable was obtained by subtracting the regressor for neutral stimuli from that for angry stimuli. Only the interaction term (i.e. the product of the time course regressor and the stimulus regressor) was raised to the second level, where a one-sample t-test was computed, which tested for a negative effect, i.e. the higher the ACC activation, the lower the amygdala activation. Note that in order to enhance the sensitivity of the PPI, it was only calculated on data from the emotion discrimination session where control processes are most evident, as an explicit processing of the emotional stimuli is required (emotion discrimination). Based on the literature (Etkin, Egner, & Kalisch, 2011) I expected to find a negative influence of the ACC on the amygdala and thus limited the search to this area (correction for multiple comparisons was based on the above mentioned amygdala masks).

6.4 Results

According to the hypothesis that training increased behavioural performance, I predicted to find significantly faster reaction times in the actors than in the sighted controls for the emotion discrimination task. In a 3x4 ANOVA a main effect of group ($F_{(2,27)}$=6.36, p<0.006, see Figure 13) was observed. As this main effect of group might stem from the previously published difference between blind and sighted, an additional two-sample t-test between sighted and actors over all 4 conditions (one-tailed due to our hypothesis) and a similar test between blind and actors (two-tailed, as we had no hypothesis) were carried out. The actors were indeed significantly faster than the sighted ($t_{(18)}$=4.38, p<0.001, Bonferroni corrected significance level: p<0.025), but showed no significant difference compared to the blind ($t_{(18)}$=0.79, p=0.429; Bonferroni corrected significance level: p=0.025). Mean reaction times (±SEM) for each group were the following: blind: 1117±53 ms, 1380±66 ms, 1152±45 ms, and 1065±51 ms; sighted controls: 1311±50 ms, 1489±67 ms, 1451±54 ms, 1311±57 ms; and actors: 1079±46 ms, 1331±67 ms, 1200±51 ms, 964±48 ms; mean RT; each for fearful, happy, neutral, and angry items, respectively.

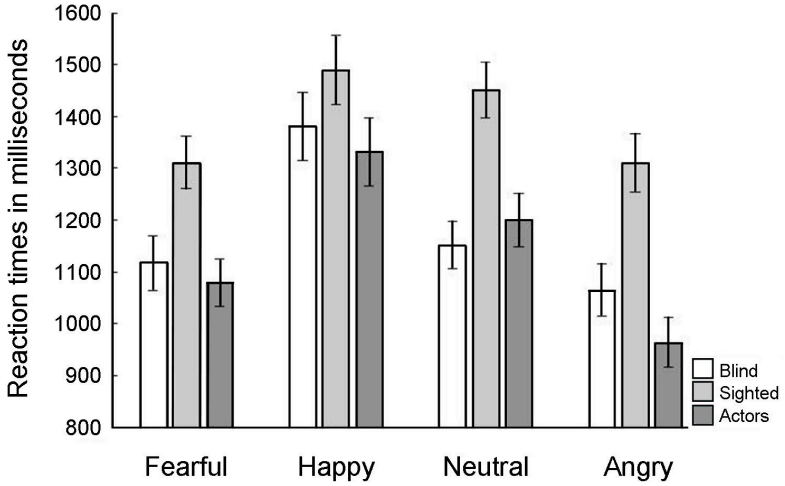

Figure 13. Mean reaction times for stimuli from all four emotional conditions in the emotion discrimination task in blind, sighted, and actors. Reaction times were recorded from stimulus onset onwards; error-bars indicate the standard error of the mean.

For the sake of completeness reaction times for each condition were also compared separately between sighted and actors (one-sided two-sample t-tests). Actors showed significantly

shorter reaction times for each emotional condition in the emotion discrimination task (fearful: $t_{(18)}$=2.46, p=0.012; happy: $t_{(18)}$=1.80, p=0.045; neutral: $t_{(18)}$=2.56, p<0.01; and angry: $t_{(18)}$=3.43, p<0.01).

While the focus was on reaction time data, accuracy data were also analysed in a similar way; note however that there was a ceiling effect with accuracy rates being very high with the blind giving (mean±SEM) 95.63±1.13 % correct answers, actors 93.67±1.60, and sighted controls 89.61±2.00%. In a 3x4 ANOVA a main effect of group ($F_{(2,27)}$=7.12, p<0.003) was observed. A two-sample t-test between sighted and actors over all 4 conditions (one-tailed due to our hypothesis) and a similar test between blind and actors (two-tailed, as we had no hypothesis) were carried out, similar to the analysis of the RT data. This time, neither actors and sighted ($t_{(18)}$=1.24, p>0.11, Bonferroni corrected significance level: p<0.025), nor actors and blind differed ($t_{(18)}$=0.99, p=0.33; Bonferroni corrected significance level: p=0.025). Note that the significant main effect in the ANOVA is driven by the previously reported difference by the blind and sighted controls for happy items.

Regarding the fMRI data I predicted to find amygdala activations to be influenced by the actors' proficiency. More specifically, I expected activation strength within the amygdala of actors to be significantly stronger than that of sighted controls and therefore tested for differences between these two groups. At a corrected level of significance, no differences in amygdala activation between the sighted and the actors in any contrast (fear > neutral and angry > neutral) could be observed. This null-finding also held when considering the data at a much more liberal uncorrected threshold of p<0.01.

The alternative hypothesis was that previous amygdala results were mainly driven by deprivation-induced plasticity. Therefore, the actors and the blind were also compared. Again, we no differences were observed at a corrected level of significance. Only when lowering the threshold to a liberal uncorrected level of p<0.01 there were differences: the blind showed stronger responses in bilateral amygdala for the contrast fearful > neutral (peak x y z in

millimetres: -20 -4 -12; $t_{(18)}$=2.82, p=0.006 uncorrected; 16 -2 -18; $t_{(18)}$=3.00, p=0.004 uncorrected) and stronger responses in the right amygdala for angry>neutral (peak x y z in millimetres: 16 -2 -16; $t_{(18)}$=2.61, p=0.009 uncorrected).

In a complementary and spatially less specific analysis that investigated the amygdala as a whole, activity strength was extracted from all voxels within the amygdala masks and then averaged over all these voxels in order to glean insight about the overall activation pattern of the amygdala. The only significant difference between actors and blind participants was found for fearful>neutral in the right amygdala ($t_{(18)}$=2.72, p=0.007) where blind participants showed stronger activation. Importantly, actors and sighted controls did not differ in any comparison (for completeness we also compared blind and sighted and observed a significant difference in the right amygdala for fearful>neutral ($t_{(18)}$=1.97, p=0.032), with blind volunteers activating more strongly, supporting our previous results (study 2).

In a previous analysis - in addition to increased amygdala activity - the blind also rated the emotional stimuli as more intense. I had no a-priori hypothesis regarding the actors' emotional intensity ratings, and therefore only conducted an exploratory analysis. As can be seen in Figure 14, the actors rated all emotions as significantly less intense than blind subjects (fearful: $t_{(18)}$=2.32, p=0.034, happy: $t_{(18)}$=4.55, p<0.001, neutral: $t_{(18)}$=2.79, p=0.013, angry: $t_{(18)}$=5.67, p<0.001).

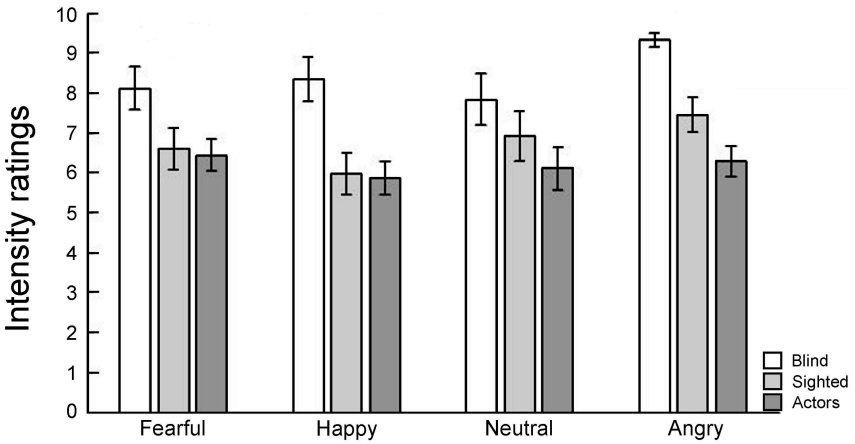

Figure 14. Mean intensity ratings for stimuli from all emotional categories in the three groups. Error bars indicate standard errors of the mean.

Importantly, they showed similar ratings to sighted controls, except for angry stimuli, which they rated significantly lower ($t_{(18)}$=2.22, p=0.041). This latter finding was completely unexpected and stands in contrast to the reaction time data, where the actors were significantly faster in classifying emotions than sighted.

This interesting finding, which may indicate a well controlled emotional response was therefore followed up further: actors clearly recognized angry stimuli as such (fast reaction times), yet they perceived them as only moderately angry (low intensity ratings). As control of emotional responses has been shown to specifically involve the anterior cingulate cortex (e.g. reappraisal, emotional conflict resolution; Etkin et al., 2011), a whole brain analysis was carried out on the contrast angry > neutral in the actors. The actors indeed showed a prominent activation of the anterior cingulate cortex (peak x y z in millimetres: -6 30 24; $t_{(9)}$=8.17, p<0.001 uncorrected). This activation was highly selective as it was not present for fearful > neutral stimuli and did not occur in the other two groups. As the ACC has been shown to have inhibitory influences on the amygdala during emotional control processes (Etkin et al., 2011), a connectivity analysis (PPI; Friston et al., 1997) was computed, which revealed that the ACC had a negative influence on activity of the actors' left amygdala (peak x y z in millimetres: -28 -6 -18; $t_{(9)}$=6.12, p<0.001 uncorrected, p=0.018 FWE corrected; Figure 15).

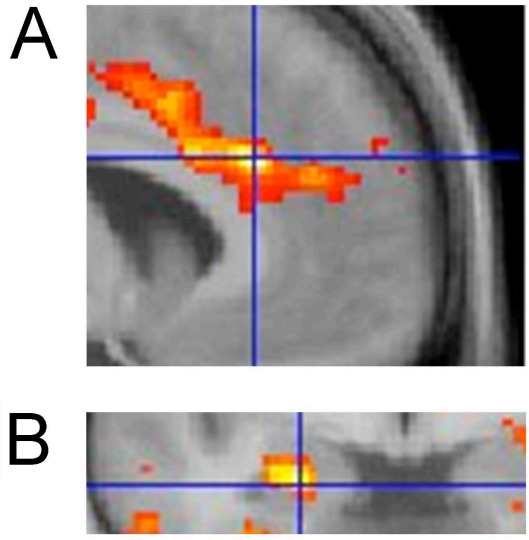

Figure 15. Group activation for angry>neutral items in actors (A). Crosshairs in this sagittal view mark the ACC (peak coordinates x y z in millimetres: -6 30 24) that was used as a seed region for the PPI analysis. (B) Crosshairs in this coronal view mark the peak coordinate within the left amygdala (-28 -6 -18) that was inversely coupled with the ACC seed region; colours indicate t-scores.

In a final control analysis, the groups' scores in several personality questionnaires were compared. There were no significant group differences in SDS or the CERQShort. In the STAI-T, only the blind and the actors differed ($t_{(18)}$=2.89, p<0.011) with actors having higher scores; there were no differences between these two groups in the PANAS. However, actors yielded higher scores in the "Negative Affect" part of the PANAS ($t_{(18)}$=2.33, p=0.03) than the sighted but did not differ in the STAI-T. Importantly, these findings had no impact on amygdala activity, as would have been expected (Kienast et al. 2008).

6.5 Summary of findings

Unexpectedly, and despite augmented behavioural performance at a comparable level to that of blind volunteers, amygdala activity in response to negatively valenced stimuli was not increased in professional actors when compared to sighted controls. This was in stalk contrast to correlated behavioural performance and increased amygdala activation in the blind (study 2) that hinted at training-induced plasticity effects within the amygdala. Intensity ratings were lower than those of blind individuals and for angry items even lower than those of sighted controls. This finding was paralleled by a down-regulation of amygdala responses via the anterior cingulate cortex, suggesting that enhanced amygdala responses in the blind (study 2) are mainly due to deprivation-induced plasticity. However, the high expertise of actors in processing emotional vocal stimuli may also be due to different neural mechanisms than in blind individuals: actors seem to process angry signals more explicitly, likely with a higher degree of cognitive control allowing them to categorize them faster than sighted individuals without any special training. By contrast, plasticity in the amygdala together with a high emotional engagement might be the essential mechanisms for the blind's superior performance.

7 Discussion

Blind people are disadvantaged in many aspects of modern daily life and are often seen as disabled or handicapped. Nevertheless, blind individuals have been shown to be superior in various behavioural tasks in diverse modalities other than vision, ranging from tactile (e.g. Braille), over auditory tasks [e.g. spatial localization (Gougoux et al., 2005; Voss et al., 2004), speech perception (Röder et al., 2002), verbal memory (Amedi et al., 2003), and olfaction (Lascano et al., 2010; Lundström et al., 2008)]. These augmented performances have been hypothesized to stem from neural plasticity (e.g. Gougoux et al., 2005), helping them to compensate for their lack in the visual domain. Neuroimaging studies provided evidence for possible neural substrates of these superior behavioural performances. Responses in the occipital cortex, a cortical area usually involved in visual processing, frequently accompanied augmented capabilities in various modality domains (Amedi et al., 2003; Büchel et al., 1998; Burton, 2003; Gougoux et al., 2005; Röder et al., 2002; Sadato et al., 1996; Weeks et al., 2000) see chapter 1 for more references). No other brain region showed such robust activation to diverse task contexts. Until now, mostly basic sensory processing has been investigated in the blind, but emotional processing has been neglected so far. This is why I presented blind, matched sighted controls and professional actors with pseudo words, spoken in different emotional tones, in an fMRI paradigm, allowing me not only to possibly expand the understanding of increased behavioural performances in the blind but also to investigate the role of the amygdala. It further enabled me to investigate the mechanisms underlying the additional OCC activations to auditory stimulation in the blind.

7.1 The amygdala & affective processing in the blind

As shown above, blind individuals are not as handicapped as they are often perceived but instead show outstanding capabilities in other domains than vision. Unfortunately however,

vision presents our dominant modality, which led some researchers to speculate about the necessity of visual experience for a normal development of various cortical functions. Studies showed however that vision is not needed for cortical areas and their functions to develop normally (Bonino et al., 2008; Mahon et al., 2009; Pietrini et al., 2004; Ricciardi et al., 2007, 2009). Consequently, mental imagery can also be excluded as an explanation for activations found in the blind during the investigated cognitive and sensory tasks. Instead, information processing in these areas seems to function modality-independently. Until now, it was unclear whether such a principle also applies to emotional processing and related responses in the amygdala, an evolutionary old structure that is heavily involved in emotional processing. If amygdala involvement in auditory emotional processing was dependent on previous visual experience, one would expect connatally blind participants not to show any amygdala activation following auditory emotional stimulation.

I found blind participants not only to outperform closely matched sighted controls in the two behavioural tasks (emotion discrimination and vowel discrimination), replicating and expanding findings of superior performance of the blind, but also to show stronger amygdala activations when presented with negatively valenced auditory stimuli. The latter finding indicates that amygdala responses to emotional signals occur even in the absence of visual emotional experience, as would be expected for an evolutionary crucial system. Therefore, activations of the amygdala cannot be attributed to visual imagery. Our data are thus in line with other studies (Bonino et al., 2008; Mahon et al., 2009; Pietrini et al., 2004; Ricciardi et al., 2007, 2009) showing that core systems develop essentially in the same way whether or not the individual has any visual experiences. Consequently, they are capable of processing information in a modality-independent fashion.

In sighted, attributions regarding the affective state of other people are predominantly based on visual, especially facial cues (Hess, Kappas, & Scherer, 1988) which have

repeatedly been shown to reliably elicit amygdala activation (e.g. Breiter et al., 1996; Morris et al., 1998; Whalen et al., 1998; for review see Costafreda et al., 2008; Phan et al., 2002). For the blind, visual information is not available and the haptic modality is usually inadequate in everyday social interactions. Thus, the auditory channel represents their primary source of sensory information in social interactions, and is of outmost relevance for the blind, resulting in a high level of training in processing auditory emotional information. Taken together with findings of reliable amygdala activation in sighted following stimulation with emotional faces (Gläscher et al., 2004; Hariri et al., 2002; Morris et al., 1996; Reinders et al., 2006), the results of enhanced amygdala activation in the blind to emotional auditory stimulation suggest that the amygdala is preferentially activated by emotional stimuli in the dominant modality.

Furthermore, one could argue that augmented auditory capabilities in the blind might account for increased amygdala activation rather than blindness per se. In this case, one would expect blind participants with better emotion discrimination abilities to show greater amygdala activation following emotional stimulation than blind participants with worse emotional discrimination skills. This is indeed what I found: In addition to superior performance in the blind and increased amygdala activation to negative emotional tones, behavioural performance (reaction times) predicted the right amygdala's response to fearful items. This finding strongly suggests that altered amygdala function is subject to functionally relevant plasticity, rather than an unspecific consequence of sensory deprivation, such as blindness. Amygdala function thus seems to not only be driven by the most reliable (and thus dominant) modality, but further to be modulated by the degree of proficiency or expertise within that modality. Having said that, I cannot exclude the possibility of deprivation-induced plastic changes within the amygdala in the blind. This point will be addressed later.

The enhanced amygdala responses I observed in the blind compared to the sighted were only evident for negatively valenced (fearful and angry) items compared to neutral stimuli but

not for happy stimuli. Emotions of fear and anger signal threat which usually requires an instant adaptation of behaviour to deal with a potentially dangerous situation (Amaral, 2002; Sander et al., 2003). Selective activation of the amygdala for angry and fearful voices is thus in agreement with the general notion of the amygdala as a relevance detector (Sander et al., 2003), as threatening and fearful voices convey essential information in social interactions. Additionally, increased amygdala activation was found in the blind irrespective of the underlying task (emotional vs. vowel discrimination task), indicating that this activation is not related to explicit emotion detection, but is rather automatically driven by the emotional valence of the stimulus. This observation supports earlier data (Fecteau et al., 2007; Jäncke et al., 2001; Quadflieg, Mohr, Mentzel, Miltner, & Straube, 2008; Vuilleumier, Armony, Driver, & Dolan, 2001), showing that amygdala related processing occurs in an automatic manner and is often not influenced by task demands. It might be possible that automatic attraction of attention to emotional auditory cues is augmented in the blind. Whether this results from a higher level of arousal, as shown in sighted volunteers (Baumgartner, Lutz, Schmidt, & Jäncke, 2006), needs to be investigated in the future.

Regarding possible confounds, the specific enhancement of BOLD responses in the amygdala to negatively valenced stimuli only cannot be explained by generally augmented behavioural performance as - taking performance as an indicator - one would also expect to find differences in amygdala activation for happy items, which was not the case. This finding stands in stalk contrast to the condition-independent increase in activation in the occipital cortex that was present in the blind, and more so than in the sighted. The independent increase in activation in bilateral occipital cortex has been reported previously for auditory and tactile tasks (Amedi et al., 2003; Büchel et al., 1998; Burton, 2003; Gougoux et al., 2005; Röder et al., 1999; Sadato et al., 1996; Weeks et al., 2000; see chapter 1 for more references). Hence, one can exclude unspecific projections from the occipital cortex to the amygdala to be causing increased amygdala activation to negatively valenced items. Differences in amygdala

activation between the two groups can neither be explained on the basis of differing personality traits (Kienast et al., 2008) as no such differences were found in the battery of personality questionnaires that all participants completed.

7.2 Plastic changes within the amygdala: Insight from actors

Based on the results obtained in study 2, one cannot clearly distinguish between two possible accounts for the increased amygdala activation in the blind to negatively valenced auditory stimuli. The amygdala's increased responses in the blind could either be due to deprivation-induced plastic changes (i.e. driven by the blind state as such) or, as suggested by a correlation found between the blinds' behavioural performance and their activity data, could result from use-dependent changes (i.e. driven by extensive training). Since professionally trained actors have undergone extensive speech and vocal training programs, especially with regard to emotional content, they should have gained a higher expertise in the auditory domain than "untrained" sighted controls have, thus presenting an ideal population to disambiguate the two possible explanations.

As hypothesized, actors performed very well in the emotion discrimination task (as well as in the vowel discrimination task), clearly outperforming sighted volunteers and showing similar reaction times as the blind in study 2. Actors have thus indeed obtained a training-induced expertise in the auditory domain, which is well supported by many previous reports of augmented behavioural performance due to auditory training in otherwise untrained individuals (e.g. Bosnyak et al., 2004; Delhommeau, Micheyl, & Jouvent, 2005; Zarate et al., 2010). Apart from this behavioural finding, the expected increase in amygdala activation in response to negatively valenced stimuli in actors failed to show. In contrast, there was even evidence for stronger amygdala responses in the blind than in the actors.

This finding clearly speaks against a major role of use-dependent plasticity in the amygdala and suggests that the previous findings in the blind (study 2) are the result of

modality dominance as a consequence of visual deprivation, i.e. deprivation-induced plastic changes. As stated earlier, sighted individuals use vision and especially facial cues with a higher precision for the attribution of affective states of others (Hess et al., 1988) and visual emotional cues have repeatedly been shown to elicit amygdala activation (e.g. Breiter et al., 1996; Morris et al., 1998; Whalen et al., 1998; for meta-analysis see e.g. Costafreda et al., 2008). Blind individuals lack the possibility to process visual input and therefore audition presents their primary source of sensory information during social interactions. For this reason, I argued that the amygdala should preferentially be activated by stimuli coming in through the dominant sensory modality, namely audition in the blind and vision in sighted humans, allowing the individual to instantly process relevant information (Amaral, 2002; Sander et al., 2003). Finding enhanced amygdala activation in the blind fits this idea. Taking the results of study 2 and 4 together, one could argue that despite the increased expertise actors have obtained in the auditory domain (as evidenced by their behavioural performance), vision still represents their dominant modality for emotion recognition and is thus more consumed with visual input. According to this line of reasoning – and contrary to my hypothesis – the amygdala of actors should thus still be predominantly modulated by visual emotional input and should thus not show increases in activation when stimulated auditorily.

As an aside, it should also be noted that actors taking part in study 4 can never be as experienced as the blind participants, as they lack years of specific auditory expertise before even entering starting drama school. The sample of actors was age-matched with the samples from study 2 in order to be able to avoid the confound of age, which can have prominent effects on the amygdala, such as volume decreases (Jack et al., 1997; Ma et al., 1999) and neurotransmitter changes (Míguez, Aldegunde, Paz-Valiñas, Recio, & Sánchez-Barceló, 1999). Matching actors and blind participants with regard to years of specific auditory expertise would have introduced a confound of age. It would further have been impossible to compare professional actors with sighted controls. Following from this it is thus conceivable

that while the actors' expertise was strong enough for performing as well as the blind in the emotion discrimination task, it was not strong enough for enhancing amygdala responses.

When investigating the emotional intensity ratings given by the actors, significantly lower ratings were observed than those of the blind and in the case of angry stimuli even lower than those of the sighted. A possible explanation for this unexpected finding comes from the way actors deal with emotional expressions professionally, i.e. when on stage: professional actors have to be able to mime emotion - in an artificial way- without actually being emotionally touched (as reported by every actor in our sample). It is therefore conceivable that this could also affect the perception of emotions. Actors may not have been as emotionally involved by our auditory emotional stimulation as the blind and hence did not show increased amygdala activations. Taking this argument even further, actors may have dealt with the stimuli in a professional way, perceiving and categorizing the emotions but using control processes to automatically distance themselves from the emotion at the same time, like they do when on stage. This might have been especially prominent in the processing of angry stimuli, which the actors discriminated as fast as the blind, but which they perceived as significantly less intense than even the sighted did.

Neurobiologically, the function of the anterior cingulate cortex has often been associated with the cognitive control of emotion (for a recent review, see Etkin et al., 2011), as for example shown in studies on voluntary emotion regulation (Eippert et al., 2007; McRae et al., 2010) and emotional conflict resolution (Egner, Etkin, Gale, & Hirsch, 2008; Etkin, Egner, Peraza, Kandel, & Hirsch, 2006). The ACC (especially the pregenual ACC and the anterior portion of the dorsal ACC) are strongly connected with affective regions, such as the amygdala (Carmichael & Price, 1995; Etkin et al., 2011). I therefore tested whether the actors would show enhanced ACC responses and indeed observed highly selective responses in the ACC for angry > neutral stimuli in the actors that were not present in the other two groups. Results from a connectivity analysis further showed that this selective activation of the ACC

was negatively correlated with amygdala activation, which is not only consistent with previous reports (Etkin et al., 2006), but might also explain the lower emotional intensity with which angry stimuli were perceived. Note however, that based on the (correlative) analysis one cannot be sure of the directionality of the negative relationship between ACC and amygdala. Previous literature suggests though that this modulation may most likely stem from inhibitory influences of the ACC on the amygdala (Etkin et al., 2006). One can thus conclude that while actors indeed profited from their trainings (as evidenced by excellent behavioural performance), this training might at the same time have served to lessen the emotional impact the stimuli have (evidenced by lower intensity ratings) and associated amygdala activity (evidenced by inhibitory ACC-amygdala connectivity). It would thus be highly interesting to see whether this finding would also be observed when actors are stimulated visually (i.e. with affective faces).

A potential limitation of study 4 is that the actors partly differed from the blind and sighted controls (having e.g. higher trait anxiety scores). This should however not pose a problem, as increased anxiety is typically associated with enhanced amygdala responses to negatively valenced events (see Ewbank et al. (2009) for a recent study). Rather, there was a specific lack of such enhanced amygdala responses in the actors.

Also, while an overwhelming majority of studies have shown that training goes along with additional and / or increased brain activations (Bangert & Altenmüller, 2003; Bosnyak et al., 2004; Elbert et al., 1995; Gaser & Schlaug, 2003; Lappe, Herholz, Trainor, & Pantev, 2008; Lotze et al., 2003; Pantev et al., 1998; Schneider et al., 2002; Shahin et al., 2003), a number of studies have also reported decreases in brain activity due to training (Haslinger et al., 2004; Jäncke, Shah, & Peters, 2000; Krings et al., 2000). It has been hypothesized that these changes could be related to more efficient neural processing, i.e. involving a smaller number of active neurons. While this is certainly a possibility, this should not be relevant for study 4, as there were no stronger responses in sighted controls than actors.

Finally, one could question our interpretation regarding the performance of blind and actors in the emotion discrimination task. Similar performances of the two groups in this measure were considered as evidence for a similar level of expertise. It is conceivable however, that the task was so easy that due to a ceiling effect in reaction times, differences between blind and actors could not be observed, wrongly suggesting comparable levels of expertise in the two groups. More difficult emotion discrimination tasks might be helpful to shed light on this question.

Combining results from 2 and 4 suggest that blindness per se seems to be the main driving-force behind plastic changes within the amygdala. Plastic changes thus seem to be deprivation-induced. It may still be that the high expertise of actors in processing emotional vocal stimuli might be due to different neural mechanisms than for blind individuals: actors seem to process angry signals more explicitly, likely with a higher degree of cognitive control allowing them to categorize them faster than sighted individuals without any special training do. By contrast, plasticity in the amygdala together with a high emotional engagement might be the essential mechanisms for the blind's superior performance.

7.3 Connectivity of the occipital cortex in the blind

In addition to the afore mentioned and discussed findings of superior behavioural performance in auditory tasks and increased amygdala activations to negatively valenced items that were further related to the individual performance in the blind, I observed additional activations of the OCC in the blind in response to non-visual stimulation, replicating earlier findings (Amedi et al., 2003; Büchel et al., 1998; Burton, 2003; Gougoux et al., 2005; Röder et al., 1999; Sadato et al., 1996; Weeks et al., 2000; for review see Merabet & Pascual-Leone, 2010). In additional analyses, significant BOLD responses were found in MGN, A1, and V1 bilaterally in both groups, which might seem surprising at first – especially

concerning the V1 activations. Note however that previous studies have shown non-visual responses in the primary visual cortex of sighted participants (Cate et al., 2009; Maeder et al., 2001; Saito et al., 2005) as well. Several studies in both animals and humans have now shown that the traditional view of unimodal primary cortices has to be reconsidered as primary cortices also respond to stimuli from other modalities, though to a lesser degree (for review see Driver & Noesselt, 2008). Concerning other group differences in activation, sighted controls showed stronger activations of the primary auditory cortex than the blind, which might again be unexpected, but has also been reported earlier (e.g. Gougoux et al., 2009). These increased activations have been linked to a more widespread auditory network towards visual areas in the blind (but see e.g. Röder et al., 1999).

Having identified enhanced V1 BOLD responses to auditory stimulation, possible pathways mediating this effect were tested next. In order to differentiate between cortico-cortical and thalamo-cortical connections mediating these activations, DCM was used to investigate the effective connectivity, i.e. the influence one brain area exerts over another (Friston, 1994). Both thalamo-cortical and cortico-cortical connections, the latter of which can further be subdivided into direct long range connections and indirect connections over multisensory areas, have been proposed as possible architectures mediating these additional OCC activations in the blind (Bavelier & Neville, 2002; Driver & Noesselt, 2008). For the present data there was clear evidence in favour of cortico-cortical connections between A1 and V1 that were stronger in the blind than in the sighted in both hemispheres. The increased connectivity between sensory cortices was very robust and also held true when performing several control analyses, such as using group-specific activation peaks or using a summary measure of individual V1 BOLD responses. Thalamo-cortical connections (MGN-V1) on the other hand did not show any consistent effects.

Only in one of the analyses there was a trend for enhanced thalamo-cortical connectivity (from MGN to V1) in the right hemisphere in the blind, but this effect did not survive correction for multiple comparisons and was not evident in either control analysis. As re-wired thalamic connections have been reported in animal literature (Frost & Moy, 1989; Kudo et al., 1997; Roe, Garraghty, Esguerra, & Sur, 1993; Sur et al., 1988), an additional DCM control analysis which comprised the lateral geniculate nucleus (LGN) instead of the MGN was carried out. Blind individuals showed a slightly decreased (though not significantly) connectivity from LGN to V1 when compared to the sighted. Based on previous findings in humans, this was however expected as a degeneration of the LGN has been reported in blind humans (Noppeney et al., 2005; Shimony et al., 2006; but see Bridge et al., 2009). This analysis provided further evidence that unspecific thalamic spill-over effects could be excluded as a possible explanation for thalamo-cortical or other connections and also indicates that auditory LGN contributions to visual cortex BOLD responses via rewired input from the inferior colliculus are unlikely. In order to get a complete view over thalamic relays in the blind, one should also include non-specific multisensory thalamic nuclei, such as the interlaminar nuclei (e.g. Berman, 1991). This was not done as such multiple differentiation of thalamic regions would necessitate high-resolution fMRI in combination with additional imaging modalities (e.g. diffusion tensor imaging) and more detailed anatomical masks. The present data thus suggest that – at least for audition – predominantly cortico-cortical connections seem to be mediating enhanced BOLD responses in the primary visual cortex of blind participants.

As already mentioned above, the measure of connectivity employed here does not allow for a differentiation between a direct (monosynaptic) pathway linking the two primary cortices and an indirect (polysynaptic) pathway via multi-sensory convergence zones. In order to do so, one would have to include candidate regions that mediate audio-visual integration and are connected to both sensory cortices in the models [such as the superior temporal

sulcus, but also parietal, pre-motor, and prefrontal regions (Driver & Noesselt, 2008)]. Further, evidence from primates indicates that direct long-range connections also exist between non-primary sensory areas (Rockland & Ojima, 2003). Therefore, these possibilities were not tested, as on the one hand model space would become extremely large, and on the other hand cytoarchitectonic information is currently not available for these areas, thus limiting objective identification. In a recent study on tactile processing in blind participants, Fujii et al. (2009) included more regions in their DCM analyses, potentially enabling them to differentiate between direct or feedback connections, which led them to favour a model comprising indirect connections between primary somatosensory cortex and primary visual cortex via parietal regions. It is important to keep in mind however that there likely are differences between modalities regarding effective connectivity between the regions involved (Driver & Noesselt, 2008). In line with this argument, a recent study of audiovisual integration showed evidence for both direct cortico-cortical and indirect cortico-cortical pathways in humans during audiovisual object categorization (Werner & Noppeney, 2010).

A finding seemingly initially at odds with the data presented is that Liu and colleagues (2007) and Yu et al. (2008) reported decreased functional connectivity in blind volunteers compared to controls between visual and auditory cortical areas during resting state fMRI. However, if one considers that the visual cortex can also be activated by auditory stimuli in sighted if the task requires high levels of attention (Cate et al., 2009), the results seem more alike: possibly, the visual cortex of blind people is predominantly recruited during demanding tasks or when relevant information is supplied (Röder, Rosler, Hennighausen, & Nacker, 1996). This would explain, why resting-state studies that pose no attentional demands fail to find such coupling (Liu et al., 2007; Yu et al., 2008), whereas activation based effective-connectivity studies do find enhanced coupling in the blind (Fujii et al., 2009). Further, other studies found attentional modulations to influence activations within the visual cortex in the

blind, thus supporting this hypothesis (Liotti, Ryder, & Woldorff, 1998; Stevens, Snodgrass, Schwartz, & Weaver, 2007).

The physiological mechanisms underlying plastic changes in cortico-cortical connectivity will have to be resolved elsewhere, as a non-invasive imaging approach was used here. Developmental changes in local connectivity [whether they may be pruning of exuberant connections, masking of silent synapses, or active inhibition (Bavelier & Neville, 2002; Maurer, Lewis, & Mondloch, 2005)] likely differ between healthy and visually deprived individuals. It has been suggested that unmasking of pre-existing connections and shifts in connectivity might underlie rapid, early plastic changes; as e.g. after a couple of days of blindfolding (Merabet et al., 2008). If sustained and reinforced, these can then lead to slower but more permanent structural changes, such as dendritic arborisation, sprouting and growth with rewiring of connections (Pascual-Leone, Amedi, Fregni, & Merabet, 2005). This line of thought would also fit with evidence of functional crossmodal sensory processing in the OCC in sighted humans (Merabet et al., 2004; Zangaladze, Epstein, Grafton, & Sathian, 1999). It may be possible, that the same connections underlie crossmodal processing in sighted but they remain comparably suppressed under conditions where vision is present (Macaluso, Frith, & Driver, 2000; Merabet et al., 2004; Zangaladze et al., 1999). The earlier the sensory loss, the more striking are the neuroplastic effects found (Hensch, 2005) One could thus say that it is the input that determines which connection gets pruned (or suppressed) and which is left unchanged (Sharma, Angelucci, & Sur, 2000; Sur et al., 1988; von Melchner, Pallas, & Sur, 2000). If a person lacks visual input, the natural pruning process could be disturbed, leaving exuberant connections, as also indicated by recent findings of increased cortical thickness in the visual cortex of blind volunteers (Jiang et al., 2009).

8 Conclusion

Taking all findings into account, my data revealed that the responsiveness of the amygdala to emotional sounds develops independently of any visual experience. Furthermore, the amygdala seems to serve the sensory modality that provides the most reliable source of emotional information and thus represents the dominant input modality. Although behavioural performance and activation of the blinds' amygdala were correlated, suggesting use-dependent changes, data of well-trained actors did not confirm this idea. Their data rather suggest that it is the deprived state that drives plastic changes within the amygdala in the blind. Alternatively one could argue that different mechanisms are responsible for augmented behavioural performance in blind volunteers on the one hand and actors on the other hand.

Using DCM I could additionally provide evidence that frequently found OCC activations in the blind in response to non-visual (in this case auditory) stimulation seem to be predominantly driven by cortico-cortical connections (as opposed to thalamo-cortical connections) that are significantly enhanced in the blind.

As stated above, blind individuals have been shown to recognize stimuli from different modalities faster or more accurately than sighted do. This pattern of results has been found in the tactile, auditory, and olfactory domain. To the best of my knowledge, affective gustatory processing in the blind has not been investigated yet. It will be interesting to see whether the blind also show enhanced amygdala responses to aversive food stimuli (Small et al., 2003), once again signalling a relevant and dangerous "event" or situation. Future studies will have to investigate the physiological mechanisms underlying these adaptive plastic changes with regard to OCC connectivity. It will further be interesting to see whether this pattern is of a more general nature, i.e. also underlies multisensory integration and will for instance hold when presenting deaf people with visual stimuli (leading to activations of auditory cortex (Finney, Clementz, Hickok, & Dobkins, 2003; Nishimura et al., 1999), which should result in

enhanced connections from V1 to A1. Finally, studies should investigate the effects of late blindness in a longitudinal manner in order to elucidate the mechanisms underlying plasticity changes within the brain over time.

Blind people may be handicapped when it comes to visual processing and vision-based interactions with the environment. Plastic changes of the cortex and the amygdala however enable them to react and interact appropriately with their surroundings and peers. Here I could show that this adaptation is based on several changes: Structures are taking over new tasks and commit to new or strengthened alliances. Further, the processing of relevant information is enhanced in the appropriate modality. These findings thus show that there are different possibilities of adaptation. While some people rely mostly on vision, others use their other senses instead. For all these adaptive changes, the brain provides the neural basis in a flexible and creative manner in order to make people accomplish great things no matter if they see or not.

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10 List of abbreviations

A1	Primary auditory cortex
ACC	anterior cingulate cortex
ANOVA	Analysis of variance
BMS	Bayesian model selection
BOLD	Blood-oxygen-level-dependent
Cerqshort	Cognitive emotion regulation questionnaire (short form)
dB	Decibel
DCM	Dynamic causal modelling
EEG	Electro-encephalogram
EMO	Emotion discrimination task
EPI	Echo planar imaging
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
FMRIB	Functional magnetic resonance imaging of the brain
FSL	FMRIB software library
FWHM	Full width at half maximum
GLM	General linear model
GRF	Gaussian random fields
HRF	Hemodynamic response function
Hz	Hertz
LCA	Leber's congenital amaurosis
LGN	Lateral geniculate nucleus
MGN	Medial geniculate nucleus
MPRAGE	Magnetization prepared rapid gradient echo

MRI	Magnetic resonance imaging
ms	Millisecond
OCC	Occipital cortex
PANAS	Positive and negative affect schedule
PPI	Psycho-physiological interaction
RF	Radio frequency
ROI	Region of interest
ROP	Retinopathy of prematurity
RP	Retinitis pigmentosa
RT	Reaction time
rTMS	Repetitive transcranial magnetic stimulation
s	Second
sd	Standard deviation
SDS	Social desirability scale
sem	Standard error of the mean
SNR	Signal to noise ratio
SPM	Statistical parametric mapping
STAI	State-traite anxiety inventory
T1	Structural brain image; high resolution
TE	Echo time
TMS	Transcranial magnetic stimulation
TR	Repetition time
V1	Primary visual cortex
V2,3,4,5	Secondary visual cortices
VOC	Vowel discrimination task

11 Appendix

11.1 Appendix 1

Table A1. Details on age, gender, handedness, educational level and visual status of blind and sighted volunteers.

Connatally blind volunteers

Age	Gender	Handedness	Education	Cause of connatal blindness
27.8	female	left	Abitur *	retinopathy of prematurity °
24.2	male	right	Abitur	genetic disorder not further specified °
29	female	right	Fachhochschulreife+	Leber's congenital amaurosis °
46.8	female	right	Abitur	prenatal retinitis
31.7	male	right	Abitur	Retinoblastoma, glass eye °
30.8	male	right	Abitur	Retinoblastoma, glass eye °
32.2	male	right	Abitur	rudimentary optic nerve °
34.5	male	right	Abitur	retinopathy of prematurity °
45.4	female	ambidextrous	mittlere Reife #	retinopathy of prematurity °
48.9	female	right	Abitur	retinopathy of prematurity °

Sighted controls

Age	Gender	Handedness	Education
26.6	female	left	Abitur
24	male	right	Abitur
30.8	female	right	Abitur
46.7	female	right	Abitur
31.6	male	right	Abitur
30.8	male	right	Abitur
31.9	male	right	Abitur
33.1	male	right	Abitur
45.4	female	right	mittlere Reife
47.7	female	right	Abitur

equivalent to:

* brit. A-levels

+ adv. technical college entrance qualification

brit. O-levels

° no residual light perception; one blind volunteer had rudimentary sensitivity for brightness differences but no pattern vision.

11.2 Appendix 2

Liebe Versuchsteilnehmerin, lieber Versuchsteilnehmer!

Vielen Dank für die Teilnahme an unserem Experiment! Hier erst einmal ein kurzer Abriss dessen, was Dich erwartet.

An jedem der vereinbarten Termine wirst Du für Pseudowörter ein Rating vornehmen, das sich auf verschiedene Aspekte dieser bezieht: zB. mußt Du angeben, ob es sich bei dem Sprecher um eine Frau oder einen Mann handelt, ob der Reiz angenehm war, welche Emotion Du meinst, herausgehört zu haben,... (das alles steht auch gleich noch einmal in der PC-Instruktion).

Wichtig ist, dass Du auf dem Display alle Bereiche genau bearbeitest, da das Ergebnis dieses Validierungsexperimentes in Folgeexperimenten direkt weiterverwendet werden soll. Es gibt einen Bereich, in dem abgefragt wird, als wie „erregend“ Du den Reiz empfunden hast. Damit ist gemeint, wie intensiv /emotional erregend der Reiz war.

Es wäre schön, wenn Du wirklich zu allen vereinbarten Terminen kommen würdest, da alle Stimuli von denselben Personen bewertet werden müssen, damit sie dann später in der Auswertung berücksichtigt werden können. Wenn Du aus irgendeinem Grund ein Termin nicht wahrnehmen kannst, sag bitte so früh wie möglich bescheid und wir machen dann einen Alternativtermin aus.

So, und jetzt erst einmal gutes Gelingen und Dankeschön!

Corinna & Maren

11.3 Appendix 3

Table A2a. Selection of the final stimulus set, including mean ratings on all rating scales of all participants for fearfully voiced stimuli.

fearful		Anger	Joy	Fear	Sadness	Neutral	Pain	Surprise	Disgust	Female	Male	Intensity								Pleasant	Arousal
												Anger	Joy	Fear	Sadness	Neutral	Pain	Surprise	Disgust		
1	mean	0	0	1	0	0	0	0	0	0,13	0,87	0	0,008	0,865	0,053	0,042	0,082	0,040	0,040	0,209	0,712
	std	0	0	0	0	0	0	0	0	0,35	0,35	0	0,037	0,162	0,124	0,185	0,202	0,099	0,184	0,234	0,309
2	mean	0	0	1	0	0	0	0	0	0	0,97	0,014	0,003	0,850	0,063	0,016	0,123	0,055	0,049	0,299	0,624
	std	0	0	0	0	0	0	0	0	0	0,18	0,045	0,018	0,144	0,179	0,053	0,219	0,112	0,187	0,274	0,252
3	mean	0	0	1	0	0	0	0	0	0	1	0,005	0,026	0,862	0,071	0,024	0,086	0,206	0,023	0,308	0,605
	std	0	0	0	0	0	0	0	0	0	0	0,020	0,105	0,155	0,194	0,074	0,191	0,300	0,125	0,234	0,296
4	mean	0	0	1	0	0	0	0	0	1	0	0,044	0	0,851	0,205	0,022	0,109	0,063	0,004	0,302	0,649
	std	0	0	0	0	0	0	0	0	0	0	0,187	0	0,120	0,322	0,084	0,125	0,151	0,015	0,285	0,245
5	mean	0	0	1	0	0	0	0	0	0,67	0,33	0,005	0,017	0,858	0,091	0,052	0,174	0,396	0,027	0,261	0,667
	std	0	0	0	0	0	0	0	0	0,48	0,48	0,025	0,067	0,137	0,186	0,168	0,280	0,389	0,072	0,197	0,235
6	mean	0	0	1	0	0	0	0	0	0,83	0,13	0,039	0,043	0,914	0,037	0,022	0,110	0,295	0,084	0,162	0,738
	std	0	0	0	0	0	0	0	0	0,38	0,35	0,087	0,185	0,126	0,107	0,066	0,251	0,339	0,235	0,217	0,308
7	mean	0	0	1	0	0	0	0	0	0,83	0,13	0,055	0,037	0,907	0,114	0,013	0,179	0,340	0,086	0,191	0,636
	std	0	0	0	0	0	0	0	0	0,38	0,35	0,193	0,183	0,086	0,262	0,047	0,287	0,370	0,202	0,168	0,334
8	mean	0	0	1	0	0	0	0	0	0,93	0,07	0,009	0,029	0,871	0,066	0,015	0,185	0,284	0,090	0,243	0,688
	std	0	0	0	0	0	0	0	0	0,25	0,25	0,049	0,147	0,159	0,175	0,053	0,279	0,356	0,243	0,236	0,275
9	mean	0	0	1	0	0	0	0	0	1	0	0,026	0,004	0,869	0,223	0,036	0,215	0,080	0,065	0,182	0,665
	std	0	0	0	0	0	0	0	0	0	0	0,094	0,015	0,157	0,341	0,102	0,346	0,213	0,197	0,222	0,331
10	mean	0	0	1	0	0	0	0	0	0	1	0,002	0,011	0,868	0,098	0,048	0,104	0,190	0,074	0,366	0,607
	std	0	0	0	0	0	0	0	0	0	0	0,010	0,053	0,125	0,206	0,162	0,203	0,264	0,220	0,259	0,316
11	mean	0	0	1	0	0	0	0	0	1	0	0	0,008	0,867	0,037	0,025	0,051	0,354	0,015	0,369	0,69
	std	0	0	0	0	0	0	0	0	0	0	0	0,024	0,123	0,108	0,082	0,164	0,321	0,068	0,230	0,304
12	mean	0	0	1	0	0	0	0	0	0	1	0,005	0,009	0,873	0,097	0,047	0,063	0,152	0,011	0,199	0,537
	std	0	0	0	0	0	0	0	0	0	0	0,019	0,050	0,112	0,220	0,127	0,139	0,259	0,041	0,172	0,276
13	mean	0	0	1	0	0	0	0	0	0	0,97	0,067	0,032	0,885	0,133	0,028	0,106	0,316	0,010	0,292	0,649
	std	0	0	0	0	0	0	0	0	0	0,19	0,254	0,138	0,103	0,286	0,083	0,256	0,353	0,033	0,283	0,286
14	mean	0	0	1	0	0	0	0	0	0	0,97	0,002	0,011	0,862	0,084	0,031	0,117	0,204	0,074	0,359	0,607
	std	0	0	0	0	0	0	0	0	0	0,18	0,010	0,053	0,128	0,199	0,093	0,220	0,299	0,22	0,253	0,316
15	mean	0	0	1	0	0	0	0	0	0	1	0,003	0,029	0,884	0,210	0,035	0,162	0,037	0,005	0,283	0,550
	std	0	0	0	0	0	0	0	0	0	0	0,018	0,117	0,108	0,261	0,091	0,247	0,116	0,026	0,231	0,294
16	mean	0	0	1	0	0	0	0	0	1	0	0,005	0,006	0,853	0,144	0,042	0,163	0,039	0,013	0,345	0,595
	std	0	0	0	0	0	0	0	0	0	0	0,030	0,019	0,151	0,219	0,146	0,233	0,100	0,055	0,242	0,270

Table A2b. Selection of the final stimulus set, including mean ratings on all rating scales of all participants for happily voiced stimuli.

happy		Anger	Joy	Fear	Sadness	Neutral	Pain	Surprise	Disgust	Female	Male	Intensity								Pleasant	Arousal
												Anger	Joy	Fear	Sad	Neutral	Pain	Surprise	Disgust		
1	mean	0	1	0	0	0	0	0,1	0,03	0	1	0,041	0,862	0,003	0,002	0,122	0,007	0,330	0	0,628	0,660
	std	0	0	0	0	0	0	0,31	0,18	0	0	0,116	0,107	0,018	0,001	0,245	0,040	0,329	0	0,247	0,249
2	mean	0	1	0	0	0	0	0,4	0	0	0,93	0	0,863	0,003	0	0,006	0,001	0,568	0	0,843	0,577
	std	0	0	0	0	0	0	0,49	0	0	0,25	0	0,114	0,015	0	0,026	0,006	0,361	0	0,160	0,282
3	mean	0	1	0	0	0	0	0,03	0	1	0	0,001	0,868	0,017	0	0,031	0,003	0,313	0,025	0,714	0,598
	std	0	0	0	0	0	0	0,18	0	0	0	0,002	0,129	0,052	0	0,100	0,016	0,309	0,139	0,281	0,247
4	mean	0	1	0	0	0	0	0,07	0	0,93	0	0	0,856	0,003	0	0,130	0,018	0,222	0	0,791	0,459
	std	0	0	0	0	0	0	0,25	0	0,25	0	0	0,159	0,016	0	0,228	0,081	0,288	0	0,204	0,292
5	mean	0	1	0	0	0	0	0,3	0,03	0,97	0,03	0,019	0,854	0,029	0,006	0,052	0,031	0,487	0,066	0,536	0,536
	std	0	0	0	0	0	0	0,47	0,18	0,18	0,18	0,050	0,188	0,105	0,037	0,160	0,109	0,353	0,162	0,267	0,257
6	mean	0	1	0	0	0	0	0,1	0	0	1	0,004	0,865	0,046	0,003	0,124	0,001	0,386	0,004	0,807	0,489
	std	0	0	0	0	0	0	0,31	0	0	0	0,020	0,177	0,194	0,011	0,220	0,005	0,332	0,019	0,177	0,269
7	mean	0	1	0	0	0	0	0,27	0	0	0,97	0,034	0,855	0,007	0,006	0,125	0,022	0,412	0,018	0,775	0,520
	std	0	0	0	0	0	0	0,45	0	0	0,18	0,182	0,136	0,027	0,024	0,239	0,100	0,361	0,100	0,169	0,303
8	mean	0	1	0	0	0	0	0	0	0	1	0	0,881	0,001	0	0,075	0,033	0,019	0,000	0,844	0,616
	std	0	0	0	0	0	0	0	0	0	0	0	0,148	0,003	0	0,168	0,183	0,059	0,001	0,141	0,267
9	mean	0	1	0	0	0	0	0,07	0	0,93	0	0,006	0,877	0,029	0	0,101	0	0,256	0,003	0,739	0,540
	std	0	0	0	0	0	0	0,25	0	0,25	0	0,033	0,100	0,147	0	0,214	0	0,308	0,018	0,215	0,288
10	mean	0	1	0	0	0	0	0,17	0	1	0	0,035	0,857	0,026	0	0,043	0,003	0,399	0,034	0,741	0,511
	std	0	0	0	0	0	0	0,38	0	0	0	0,182	0,202	0,111	0	0,097	0,016	0,328	0,182	0,258	0,274
11	mean	0	1	0	0	0	0	0,1	0	0	0,97	0,001	0,859	0,002	0,002	0,070	0,011	0,177	0,001	0,834	0,585
	std	0	0	0	0	0	0	0,31	0	0	0,18	0,001	0,176	0,009	0,009	0,127	0,059	0,317	0,005	0,231	0,308
12	mean	0	1	0	0	0	0	0,23	0	0	0,97	0	0,853	0	0,000	0,124	0	0,428	0	0,827	0,463
	std	0	0	0	0	0	0	0,43	0	0	0,18	0	0,134	0	0,002	0,255	0	0,351	0	0,145	0,274
13	mean	0	1	0	0	0	0	0,13	0	1	0	0,003	0,887	0,004	0,003	0,196	0,001	0,230	0,002	0,780	0,540
	std	0	0	0	0	0	0	0,35	0	0	0	0,002	0,103	0,015	0,011	0,220	0,012	0,330	0,011	0,202	0,310
14	mean	0	1	0	0	0	0	0,23	0	0,90	0,03	0,016	0,863	0,057	0,002	0,046	0,004	0,416	0,034	0,641	0,574
	std	0	0	0	0	0	0	0,43	0	0,31	0,18	0,088	0,139	0,188	0,011	0,109	0,024	0,348	0,168	0,277	0,233
15	mean	0	1	0	0	0	0	0,07	0	1	0	0,037	0,887	0,044	0	0,046	0,017	0,357	0,044	0,704	0,546
	std	0	0	0	0	0	0	0,25	0	0	0	0,183	0,141	0,185	0	0,108	0,055	0,352	0,190	0,259	0,286
16	mean	0	1	0	0	0	0	0,13	0	1	0	0,003	0,887	0,004	0,003	0,110	0,002	0,304	0,002	0,780	0,540
	std	0	0	0	0	0	0	0,35	0	0	0	0,012	0,103	0,014	0,011	0,220	0,012	0,330	0,011	0,202	0,310

Table A2c. Selection of the final stimulus set, including mean ratings on all rating scales of all participants for neutrally voiced stimuli.

neutral		Anger	Joy	Fear	Sadness	Neutral	Pain	Surprise	Disgust	Female	Male	Intensity								Pleasant	Arousal
												Anger	Joy	Fear	Sad	Neutral	Pain	Surprise	Disgust		
1	mean	0	0	0	0	1	0	0	0	0	1	0,063	0,037	0,019	0,036	0,881	0,016	0,008	0,064	0,552	0,222
	std	0	0	0	0	0	0	0	0	0	0	0,145	0,113	0,104	0,182	0,231	0,057	0,027	0,209	0,241	0,245
2	mean	0	0	0	0	1	0	0	0	1	0	0,046	0,018	0,002	0	0,888	0,010	0,003	0,029	0,579	0,220
	std	0	0	0	0	0	0	0	0	0	0	0,129	0,064	0,013	0	0,221	0,053	0,016	0,098	0,225	0,228
3	mean	0	0	0	0	1	0	0	0	0	1	0,038	0,019	0,002	0,007	0,895	0,018	0	0	0,655	0,242
	std	0	0	0	0	0	0	0	0	0	0	0,084	0,095	0,012	0,023	0,153	0,077	0	0	0,225	0,263
4	mean	0	0	0	0	1	0	0	0	1	0	0,025	0,008	0,007	0,031	0,863	0,004	0,002	0,024	0,5925	0,279
	std	0	0	0	0	0	0	0	0	0	0	0,052	0,032	0,039	0,136	0,254	0,012	0,006	0,075	0,266	0,282
5	mean	0	0	0	0	1	0	0	0	0	1	0,010	0,030	0,016	0,015	0,951	0,018	0,003	0,004	0,709	0,216
	std	0	0	0	0	0	0	0	0	0	0	0,039	0,096	0,086	0,071	0,099	0,096	0,018	0,018	0,209	0,229
6	mean	0	0	0	0	1	0	0	0	0,97	0	0,028	0,001	0,020	0,066	0,869	0,067	0,013	0,036	0,613	0,239
	std	0	0	0	0	0	0	0	0	0,18	0	0,076	0,003	0,080	0,199	0,236	0,214	0,068	0,183	0,259	0,247
7	mean	0	0	0	0	1	0	0	0	0	1	0,071	0,048	0	0	0,852	0,005	0,026	0,027	0,654	0,234
	std	0	0	0	0	0	0	0	0	0	0	0,218	0,166	0	0	0,243	0,021	0,085	0,083	0,225	0,245
8	mean	0	0	0	0	1	0	0,03	0	0,93	0,07	0,010	0,048	0,043	0,038	0,883	0,010	0,027	0,077	0,483	0,283
	std	0	0	0	0	0	0	0,18	0	0,25	0,25	0,039	0,143	0,184	0,100	0,167	0,036	0,106	0,193	0,248	0,323
9	mean	0	0	0	0	1	0	0	0	0	1	0,071	0,048	0	0	0,852	0,005	0,026	0,027	0,654	0,234
	std	0	0	0	0	0	0	0	0	0	0	0,218	0,166	0	0	0,243	0,021	0,085	0,083	0,225	0,245
10	mean	0	0	0	0	1	0	0,03	0	0,3	0,7	0,006	0,028	0,047	0,042	0,879	0,032	0,077	0,043	0,577	0,195
	std	0	0	0	0	0	0	0,18	0	0,47	0,47	0,023	0,124	0,153	0,115	0,111	0,151	0,230	0,184	0,224	0,210
11	mean	0	0	0	0	1	0	0	0	0	1	0,027	0,079	0,028	0,041	0,864	0,042	0,059	0,034	0,731	0,197
	std	0	0	0	0	0	0	0	0	0	0	0,091	0,224	0,088	0,102	0,223	0,140	0,138	0,129	0,230	0,228
12	mean	0	0	0	0	1	0	0,03	0	1	0	0,048	0,016	0,007	0,013	0,882	0,009	0,029	0,039	0,600	0,212
	std	0	0	0	0	0	0	0,18	0	0	0	0,128	0,045	0,031	0,070	0,214	0,029	0,102	0,161	0,247	0,253
13	mean	0	0	0	0	1	0	0	0	0	1	0,082	0,032	0,018	0,056	0,887	0,016	0,038	0,031	0,610	0,252
	std	0	0	0	0	0	0	0	0	0	0	0,159	0,104	0,097	0,204	0,152	0,088	0,107	0,106	0,238	0,273
14	mean	0	0	0	0	1	0	0	0	1	0	0,112	0,008	0,003	0,014	0,851	0,021	0	0,047	0,542	0,175
	std	0	0	0	0	0	0	0	0	0	0	0,269	0,029	0,010	0,044	0,215	0,066	0	0,172	0,247	0,211
15	mean	0	0	0	0	1	0	0	0	0	0,9	0	0,104	0,003	0,062	0,873	0,002	0,056	0,001	0,759	0,259
	std	0	0	0	0	0	0	0	0	0	0,31	0	0,212	0,018	0,142	0,192	0,010	0,193	0,005	0,197	0,253
16	mean	0	0	0	0	1	0	0	0	1	0	0	0,046	0,040	0,050	0,858	0,027	0,044	0,001	0,658	0,172
	std	0	0	0	0	0	0	0	0	0	0	0	0,147	0,112	0,115	0,205	0,084	0,106	0,004	0,241	0,206

Table A2d. Selection of the final stimulus set, including mean ratings on all rating scales of all participants for angrily voiced stimuli.

angry		Anger	Joy	Fear	Sadness	Neutral	Pain	Surprise	Disgust	Female	Male	Intensity								Pleasant	Arousal
												Anger	Joy	Fear	Sad	Neutral	Pain	Surprise	Disgust		
1	mean	1	0	0	0	0	0	0	0	0	1	0,922	0,001	0,041	0,025	0,014	0,084	0,076	0,061	0,099	0,790
	std	0	0	0	0	0	0	0	0	0	0	0,145	0,005	0,123	0,108	0,050	0,193	0,192	0,162	0,135	0,263
2	mean	1	0	0	0	0	0	0	0	1	0	0,840	0,036	0,049	0,020	0,038	0,053	0,084	0,137	0,183	0,692
	std	0	0	0	0	0	0	0	0	0	0	0,166	0,183	0,198	0,085	0,093	0,122	0,192	0,264	0,236	0,288
3	mean	1	0	0	0	0	0	0	0	1	0	0,711	0,033	0,036	0,039	0,066	0,060	0,056	0,234	0,142	0,719
	std	0	0	0	0	0	0	0	0	0	0	0,317	0,183	0,094	0,136	0,169	0,163	0,154	0,354	0,144	0,281
4	mean	1	0	0	0	0	0	0	0	1	0	0,876	0,015	0,033	0,070	0,030	0,112	0,048	0,253	0,114	0,760
	std	0	0	0	0	0	0	0	0	0	0	0,133	0,079	0,070	0,170	0,068	0,219	0,157	0,318	0,127	0,279
5	mean	1	0	0	0	0	0	0	0	0,87	0,13	0,829	0,035	0,051	0,013	0,074	0,042	0,077	0,066	0,230	0,727
	std	0	0	0	0	0	0	0	0	0,35	0,35	0,215	0,183	0,186	0,036	0,254	0,117	0,161	0,185	0,233	0,302
6	mean	1	0	0	0	0	0	0	0	0,90	0,07	0,768	0,004	0,056	0,053	0,057	0,069	0,103	0,210	0,172	0,733
	std	0	0	0	0	0	0	0	0	0,31	0,25	0,296	0,017	0,207	0,198	0,189	0,219	0,243	0,334	0,171	0,286
7	mean	1	0	0	0	0	0	0	0	0,90	0,10	0,780	0,032	0,035	0,003	0,021	0,048	0,078	0,072	0,203	0,699
	std	0	0	0	0	0	0	0	0	0,31	0,31	0,261	0,142	0,102	0,018	0,052	0,140	0,169	0,162	0,202	0,307
8	mean	1	0	0	0	0	0	0	0	1	0	0,896	0,002	0,038	0,001	0,001	0,025	0,058	0,083	0,134	0,703
	std	0	0	0	0	0	0	0	0	0	0	0,180	0,012	0,125	0,005	0,004	0,080	0,112	0,179	0,129	0,332
9	mean	1	0	0	0	0	0	0	0	0	1	0,788	0	0,035	0,006	0,022	0,067	0,033	0,119	0,118	0,726
	std	0	0	0	0	0	0	0	0	0	0	0,299	0	0,106	0,033	0,069	0,198	0,120	0,270	0,176	0,317
10	mean	1	0	0	0	0	0	0	0	0	0,97	0,833	0,013	0,027	0,022	0,022	0,042	0,022	0,167	0,086	0,725
	std	0	0	0	0	0	0	0	0	0	0,19	0,219	0,048	0,117	0,106	0,087	0,135	0,095	0,288	0,126	0,302
11	mean	1	0	0	0	0	0	0	0	0	1	0,775	0,014	0,005	0,008	0,010	0,083	0,032	0,101	0,226	0,603
	std	0	0	0	0	0	0	0	0	0	0	0,296	0,060	0,020	0,028	0,032	0,258	0,089	0,239	0,235	0,351
12	mean	1	0	0	0	0	0	0,03	0	0	0,97	0,758	0,097	0,019	0,005	0,011	0,058	0,136	0,150	0,213	0,594
	std	0	0	0	0	0	0	0,18	0	0	0,18	0,272	0,268	0,106	0,019	0,039	0,183	0,255	0,308	0,222	0,335
13	mean	1	0	0	0	0	0	0,03	0	0,57	0,43	0,789	0,009	0,029	0,006	0,047	0,032	0,106	0,066	0,261	0,581
	std	0	0	0	0	0	0	0,19	0	0,50	0,50	0,232	0,042	0,111	0,022	0,151	0,082	0,202	0,146	0,241	0,334
14	mean	1	0	0	0	0	0	0,03	0	0	1	0,924	0,037	0,042	0,004	0,037	0,053	0,093	0,066	0,171	0,723
	std	0	0	0	0	0	0	0,19	0	0	0	0,098	0,182	0,186	0,022	0,183	0,191	0,191	0,144	0,188	0,307
15	mean	1	0	0	0	0	0	0	0	0	1	0,858	0,003	0,025	0,022	0,019	0,062	0,159	0,064	0,246	0,701
	std	0	0	0	0	0	0	0	0	0	0	0,167	0,018	0,100	0,077	0,046	0,160	0,286	0,160	0,265	0,292
16	mean	1	0	0	0	0	0	0	0	0	1	0,890	0,003	0,042	0,019	0,030	0,062	0,090	0,100	0,150	0,737
	std	0	0	0	0	0	0	0	0	0	0	0,141	0,018	0,111	0,093	0,100	0,154	0,211	0,214	0,167	0,277

11.4 Appendix 4

Description of personality questionnaires

Social desirability scale (SDS). The SDS (Crowne & Marlowe, 1960; Lueck & Timaeus, 1969) was developed because psychologists realized that personality tests were/are vulnerable to socially desirable responding through which the approval of other people should be achieved, limiting the predictive validity of these tests. The scale contains true-false items, which on the one hand describe both acceptable but improbable behaviours, and on the other hand it includes items seen as unacceptable but probable. If individuals affirm to "good" items, they claim something very improbable about themselves whilst the rejection of "bad" items account for a denial of common human failings. The SDS is thus a scale indirectly measuring the need for approval. This questionnaire was introduced into this study as I wanted to make sure that participants from both groups were equally honest in their ratings of the emotional stimuli.

Cognitive emotion regulation questionnaire (CERQshort). The CERQshort is the short version (18 items) of the original cognitive emotion regulation questionnaire (CERQ; Garnefski, Kraaij, & Spinhoven, 2001). In both versions, nine different cognitive coping strategies people tend to use having experienced negative life events are differentiated: self-blame, other-blame, focus on thought (i.e. rumination), catastrophizing, positive refocusing, planning, positive reappraisal, putting into perspective, and acceptance) , only the number of items per scale differs (four vs. two). Coping strategies seem to play an important role in the relationship between the experience of negative life events and the reporting of symptoms of depression and anxiety. I included this personality questionnaire in the study in order to ensure that group differences in brain activity (especially within the amygdala) could not be related to differences in personally traits regarding negative experiences. This was especially

important as blindness may be seen as a severe handicap or negative life event that might in turn influence the way one deals with other negative events.

Positive and negative affect schedule (PANAS). The positive and negative affect schedule contains 20 adjectives describing different affective states. Participants have to indicate how strongly they have experiences this very feeling on a 5 point scale over the last year or so. It is thus a psychometric self-report measure of positive and negative affect (developed by Watson, Clark, and Tellegen; 1988) which have been shown to relate to other personality states and traits, such as anxiety or depression. Negative and positive affect reflect dispositional dimensions. Positive and negative affect are supposed to be measured independently when using this scale (but while they have been shown to be distinct, they are nevertheless negatively correlated in a moderate way; J R. Crawford and J D. Henry; British Journal of Clinical Psychology (2004). This scale was used here because I wanted to make sure that participants of the two groups did not differ in any emotional way which might in turn influence functional imaging data.

State-Trait Anxiety Inventory (STAI Trait). The STAI ((Laux, Glanzmann, Schaffner, & Spielberger, 1981; Spielberger, Gorsuch, & Lushene, 1970) is a personality questionnaire which captures both the current state anxiety and the habitual anxiety. These two types of anxiety can be detected independently, containing 20 items each that can be answered on a 4 point scale. In the present work, only the trait part was used. It contains questions that describe the general condition, irrespective of the present situation. I introduced this form in order to differentiate whether each participant had an underlying anxiety disposition that might account for possible differences found, as it has been shown that underlying differences in e.g. trait anxiety may lead to increased activations of the amygdala (Kienast et al., 2008). It was important to rule out this possible confound which could potentially lead to groups differences in amygdala activation.

11.5 Appendix 5

Liebe Versuchsteilnehmerin, lieber Versuchsteilnehmer,

vielen Dank für die Teilnahme an meinem Experiment! Im Folgenden werde ich Ihnen beschreiben, wie das Experiment aufgebaut ist und was Ihre Aufgabe sein wird.

Der Versuch ist in verschiedene Teile gegliedert.

Im 1. Teil werden wir die Aufgabe außerhalb des MRT trainieren. In mehreren Durchgängen wird Ihnen über Kopfhörer ein Warnton präsentiert, dem ein Phantasiewort folgt. Dieses Wort kann z.B. „baba“ oder „gigo“ etc. sein.

In relativ kurzen Abständen werden Ihnen mehrere dieser Wörter vorgespielt und Ihre Aufgabe ist, **in dem einen Block**, anzugeben, ob es **ängstlich, fröhlich, neutral oder wütend ausgesprochen wurde**, unabhängig davon, um was für ein Wort es sich dabei handelt und ob der Sprecher männlich oder weiblich war. Den einzelnen Emotionen sind hierfür bestimmte Knöpfe/Tasten zugeteilt.

In einem anderen Block sollen Sie unabhängig von der Emotion **die 1. Vokale** innerhalb der Wörter **erkennen (a, e, i, o)**; hier sind auch wieder bestimmte Knöpfe/Tasten für die einzelnen Vokale vorgesehen.

Danach müssen verschiedene Formblätter ausgefüllt und ein MR-Arzt aufgesucht werden.

Im Anschluss geht es dann in den Scanner. Bevor es mit dem eigentlichen Experiment losgeht, müssen jedoch verschiedene Messungen gemacht werden, bei denen Sie einfach nur still liegen müssen. Diese dauern nicht lange. Das Experiment läuft folgendermaßen ab: zuerst machen wir einen Lautstärke-Test, damit die für Sie beste Lautstärke ermittelt und eingestellt werden kann. Ihre Aufgabe während des Versuches wird dieselbe sein wie im Training: in einem Block gilt es, auf die gehörte Emotion mit der richtigen Taste zu reagieren; in dem anderen Block soll der jeweils 1. Vokal erkannt werden. Die Reihenfolge der Blöcke und auch die Fingerverteilung werde ich jeweils vor der Messung noch einmal mitteilen.

Nach der Messung muss dann noch ein anderen Aufgabe durchgeführt werden und verschiedene Fragebögen ausgefüllt werden.

Während des Experiments möchten ich Sie bitten, auf Folgendes zu achten:

- Bitte bewegen Sie sich so wenig wie möglich; vor allem nicht den Kopf (in den längeren Pausen zwischen den drei Versuchsteilen können Sie sich bewegen).
- Bitte reagieren Sie so schnell, aber auch so genau wie möglich.

Nun noch einige Informationen zur Vorbereitung:

- Legen Sie bitte alle metallischen Gegenstände (Uhr, Schmuck, Geld, Gürtel etc.) in die dafür vorgesehenen Schließfächer. Bitte auch magnetische Karten usw. ablegen!

Wenn es noch irgendwelche Unklarheiten gibt, fragen Sie mich bitte!

Vielen Dank noch einmal für die Teilnahme!

Corinna

11.6 Appendix 6

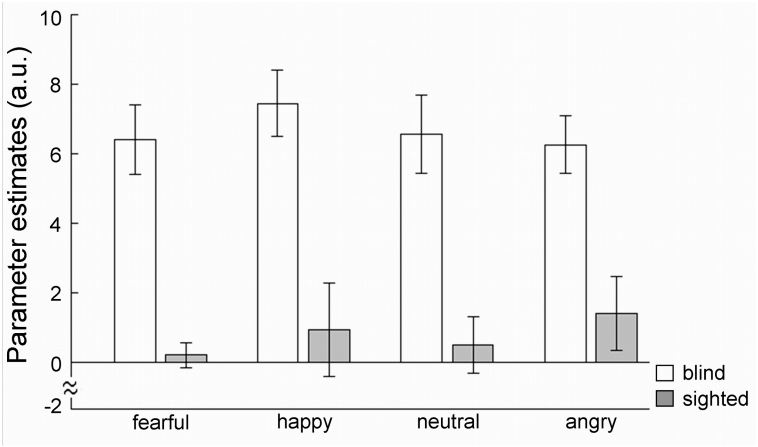

Figure A1. Mean parameter estimates of occipital activation in both blind and sighted for each emotional category. Parameter estimates were extracted from all suprathreshold voxels within a 40mm sphere around the seed region (x, y, z in mm: 0, -84, 12).

11.7 Appendix 7

Table A3. Greater occipital cortex activation in blind as compared to sighted volunteers in response to all stimuli, regardless of the emotional category or task. Coordinates are denoted by x, y, z in mm (MNI space). Correction was based on a search volume of a 40 mm diameter sphere centred anatomically in the midline of the occipital lobe at 0, -84, 12 mm.

Region	**x, y, z**	$t_{(18)}$	p FWE-corr
R superior occipital gyrus	20, -92, 30	8.34	<0.002
R superior occipital gyrus	22, -88, 28	8.21	<0.003
R middle occipital gyrus	32, -92, 10	7.73	<0.005
R middle occipital gyrus	28, -94, 16	7.68	<0.006
R fusiform gyrus	26, -64, -10	6.99	<0.015
R middle occipital gyrus	28, -74, 24	6.89	<0.016
R cuneus	22, -96, 10	6.79	<0.019

11.8 Appendix 8

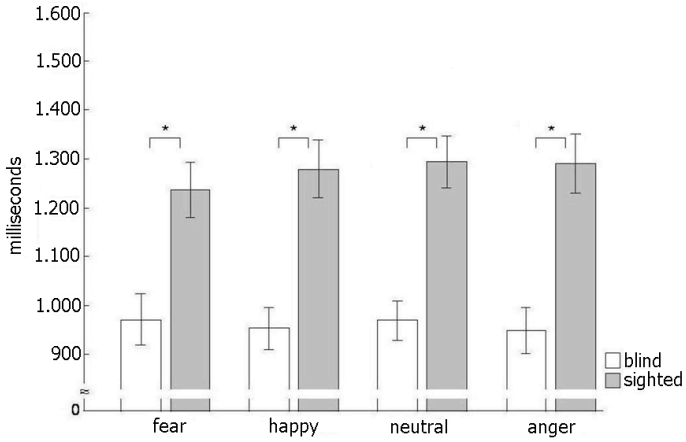

Figure A2. Mean reaction times for stimuli in the vowel discrimination task of both blind and sighted volunteers for each emotional category. Reaction times were recorded from stimulus onset onwards. The blind were significantly faster than the sighted in all conditions.

11.9 Appendix 9

Table A4. Reaction time data			
Factors that reached significance	**df**	**F value**	***p* value**
GROUP	F(1,18)	14.16	<0.001
EMO x VOC	F(1,18)	11.91	<0.003
COND	F(3,54)	16.96	<0.001
GROUP x COND	F(3,54)	2.828	<0.050
TASK x COND	F(3,54)	24.75	<0.001
GROUP x TASK x COND	F(3,54)	3.45	<0.030
RT EMO TASK only			
GROUP	F(1,18)	7.05	<0.020
COND	F(3,54)	26.00	<0.001
GROUP x COND	F(3,54)	3.44	<0.030
RT VOC TASK only			
GROUP	F(1,18)	12.22	<0.003

11.10 Appendix 10

Table A5. Accuracy data.			
Factors that reached significance	**df**	**F value**	***p* value**
GROUP	F(1,18)	9.53	<0.007
TASK	F(1,18)	24.60	<0.001
GROUP x TASK	F(1,18)	9.83	<0.006
COND	F(3,54)	28.75	<0.001
GROUP x COND	F(3,54)	6.30	<0.001
TASK x COND	F(3,54)	27.09	<0.001
GROUP x TASK x COND	F(3,54)	6.58	<0.001
ACC EMO task only			
GROUP	F(1,18)	12.57	<0.003
COND	F(3,54)	31.87	<0.001
GROUP x COND	F(3,54)	7.42	<0.001
ACC VOC task only	no significant differences		

11.11 Appendix 11

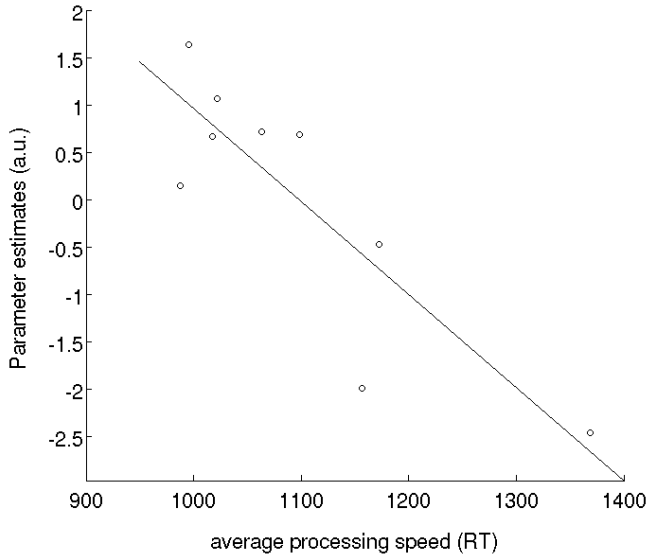

Figure A3. Prediction of BOLD response of blind volunteers on the basis of reaction times in the emotion discrimination task after the removal of an outlier in the blind group. Shorter reaction times to fearful stimuli in the blind were related to greater amygdala activation (peak x, y, z in mm: 30, 4, -22).

11.12 Appendix 12

Table A6. List of individual coordinates from which time-series were extracted for each participant. Coordinates are denoted by x, y, z in mm (MNI-space). An "x" after the coordinates denotes non-significant responses in the search volume for that participant. In each of those cases (11 of a total of 120), the group peak was chosen.

Group	**MGN left**				**MGN right**				**A1 left**				**A1 right**				**V1 left**				**V1 right**			
	x	**y**	**z**		**x**	**y**	**z**		**x**	**y**	**z**		**x**	**y**	**z**		**x**	**y**	**z**		**x**	**y**	**z**	
blind	-14	-26	-6		18	-26	-4		-56	-14	6		54	-14	6		-10	-72	10		0	-74	6	
sighted	-16	-26	-6		16	-24	-6		-54	-12	0		50	-20	8		-8	-78	12		6	-82	10	
blind	-16	-28	-6		18	-26	-6		-54	-16	6		54	-12	2		-14	-74	6		10	-84	6	
blind	-16	-26	-6		16	-24	-6	x	-56	-14	4		56	-12	6		-2	-76	2		2	-84	2	
blind	-14	-26	-6	x	18	-24	-6		-52	-18	6		54	-12	2		-10	-72	6		0	-78	2	
blind	-16	-28	-8		18	-26	-4		-56	-14	4		56	8	2		-12	-70	6		6	-80	2	
sighted	-14	-28	-6		16	-24	-6	x	-56	-14	6		56	-8	2		-6	-70	2		0	-76	8	
blind	-14	-26	-6		16	-26	-6		-50	-18	4		54	-10	2		-6	-72	6		6	-80	2	
sighted	-14	-26	-6	x	16	-24	-10		-54	-16	6		52	-16	4		-10	-72	10		4	-80	8	x
sighted	-14	-28	-6		16	-26	-8		-50	-18	6		52	-16	4		-2	-78	2		0	-78	2	
blind	-14	-28	-6		16	-26	-8		-56	-14	4		54	-14	8		-6	-78	8		10	-80	6	
sighted	-14	-26	-8		16	-26	-6		-50	-18	4		54	-16	4		-4	-78	12		10	-80	6	
blind	-14	-26	-6	x	16	-26	-6		-54	-12	0		56	-10	4		-2	-80	6		2	-82	6	
blind	-16	-24	-8		18	-24	-6		-56	-8	2		56	-12	6		-14	-74	6		0	-84	8	
sighted	-14	-26	-6	x	16	-24	-6	x	-52	-16	6		54	-18	6		-12	-70	8		2	-78	2	
blind	-14	-26	-6		16	-24	-6	x	-48	-16	0		54	-12	2		-8	-78	0		2	-80	4	
sighted	-14	-28	-6		16	-28	-6		-52	-18	8		56	-14	8		-2	-80	8		0	-82	10	
sighted	-14	-28	-8		18	-26	-6		-52	-18	6		54	-16	4		-10	-72	12		10	-82	12	
sighted	-14	-28	-6		18	-26	-8		-54	-16	6		52	-18	4		-14	-74	6		2	-76	2	
sighted	-14	-26	-6	x	16	-24	-6	x	-56	-12	6		54	-16	8		-2	-72	12		8	-84	10	

11.13 Appendix 13

Table A7. Results of the analysis testing for group differences (two-sample t-test). Coordinates are denoted in mm (MNI-space). Corrected p-values refer to the respective search volume (based on cytoarchitectonic probability maps). No significant differences in activation were observed in the MGN. Abbreviations: medial geniculate nucleus (MGN), primary auditory cortex (A1), primary visual cortex (V1). The peaks in plain typeface are part of the same cluster, the main peak of which is set in bold typeface.

Left hemisphere					**Right hemisphere**			
Sighted > Blind								
	coordinates	**$t_{(18)}$**	**p** (uncorr.)	**p** (corr.)	**coordinates**	**$t_{(18)}$**	**p** (uncorr.)	**p** (corr.)
A1	**-44 -18 6**	**3.32**	**0.002**	**0.087**	**50 -8 4**	**3.66**	**0.001**	**0.056**
					50 -20 8	**2.89**	**0.005**	**0.185**
Blind > Sighted								
V1	**-8 -102 16**	**4.01**	**0.000**	**0.135**	**20 -100 10**	**6.03**	**0.000**	**0.007**
	-6 -80 2	**3.98**	**0.000**	**0.142**	16 -98 14	5.37	0.000	0.020
	-2 -86 4	3.27	0.002	0.373	28 -98 2	5.24	0.000	0.025
					16 -82 2	5.14	0.000	0.029
					14 -94 -6	4.83	0.000	0.049
					24 -96 -6	4.33	0.000	0.109
					6 -88 -2	3.70	0.001	0.274
					10 -92 4	3.66	0.001	0.290
					6 -92 14	3.19	0.003	0.502
					2 -94 10	**2.92**	**0.005**	**0.647**

11.14 Appendix 14

Table A8. Results of the conjunction analysis across both groups (blind & sighted). Coordinates are denoted in mm (MNI-space). Corrected p-values refer to the respective search volume (based on cytoarchitectonic probability maps). Abbreviations: medial geniculate nucleus (MGN), primary auditory cortex (A1), and primary visual cortex (V1).

	Left hemisphere				**Right hemisphere**			
	Coordinates	**$t_{(18)}$**	**p** (uncorr.)	**p** (corr.)	**Coordinates**	**$t_{(18)}$**	**p** (uncorr.)	**p** (corr.)
MGN	-14 -26 -6	3.11	0.003	0.014	16 -24 -6	3.9	0.001	0.004
A1	-54 -14 2	9.73	0.000	0.000	54 -14 6	9.71	0.000	0.000
V1	-6 -74 6	3.9	0.001	0.160	4 -80 8	3.7	0.001	0.275

11.15 Appendix 15

Table A9. Parameter estimates of inputs and intrinsic connections for each group and hemisphere. The p-values refer to the within-group test (two-tailed one-sample t-test). To survive correction for multiple comparisons (Bonferroni), the p-value has to fall below 0.009.

	Left hemisphere					**Right hemisphere**			
Parameter	**Blind**		**Sighted**			**Blind**		**Sighted**	
	Mean ± SEM	p	Mean ± SEM	p		Mean ± SEM	p	Mean ± SEM	p
Input MGN	1.05 ± 0.24	0.002	1.16 ± 0.24	0.001		1.16 ± 0.11	0.000	1.03 ± 0.29	0.006
MGN-A1	0.63 ± 0.16	0.004	0.55 ± 0.20	0.024		0.77 ± 0.06	0.000	0.50 ± 0.21	0.042
A1-MGN	-0.10 ± 0.03	0.010	-0.16 ± 0.09	0.087		-0.15 ± 0.02	0.000	-0.17 ± 0.10	0.143
MGN-V1	0.24 ± 0.11	0.047	0.29 ± 0.11	0.022		0.40 ± 0.04	0.000	0.23 ± 0.09	0.030
V1-MGN	-0.10 ± 0.04	0.038	-0.01 ±0.02	0.797		-0.17 ± 0.02	0.000	-0.05 ± 0.02	0.058
A1-V1	0.25 ± 0.07	0.004	0.05 ± 0.05	0.364		0.29 ± 0.05	0.000	0.10 ± 0.04	0.021
V1-A1	0.15 ± 0.05	0.020	0.24 ± 0.10	0.046		0.16 ± 0.05	0.007	0.18 ± 0.09	0.074

11.16 Appendix 16

Table A10. Results of the control analysis that only included participants with significant responses in the search volumes. Only within-group parameter estimates of inputs and intrinsic connections for each hemisphere (mean ± standard error) and their significance are reported; for between-group results, please see the main text.

	Left hemisphere				**Right hemisphere**			
	Blind	**Sighted**	**t**	**p**	**Blind**	**Sighted**	**t**	**p**
Input	1.25 ± 0.14	1.47 ± 0.18	-0.88	0.397	1.26 ± 0.09	1.46 ± 0.18	-0.88	0.397
MGN-A1	0.77 ± 0.06	0.70 ± 0.11	0.50	0.628	0.78 ± 0.06	0.74 ± 0.09	0.37	0.718
MGN-V1	0.33 ± 0.09	0.37 ± 0.13	-0.22	0.584	0.39 ± 0.05	0.37 ± 0.11	0.18	0.431
A1-V1	0.25 ± 0.08	0.02 ± 0.07	2.07	0.029	0.31 ± 0.06	0.06 ± 0.03	3.58	0.002

11.17 Appendix 17

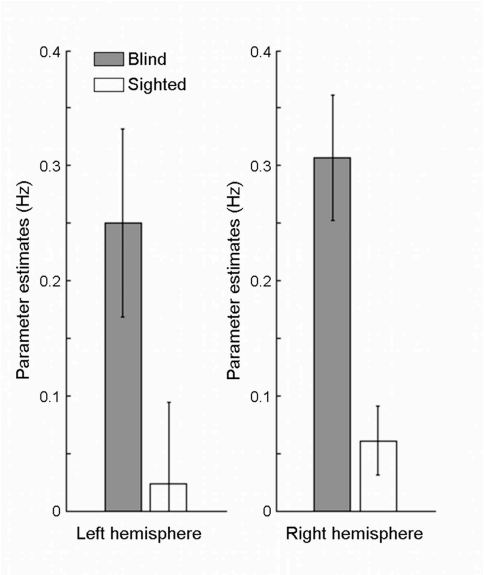

Figure A4. Connection from primary auditory cortex (A1) to primary visual cortex (V1) in a control analysis. Only participants who showed significant responses in the search volumes were included in this analysis.

11.18 Appendix 18

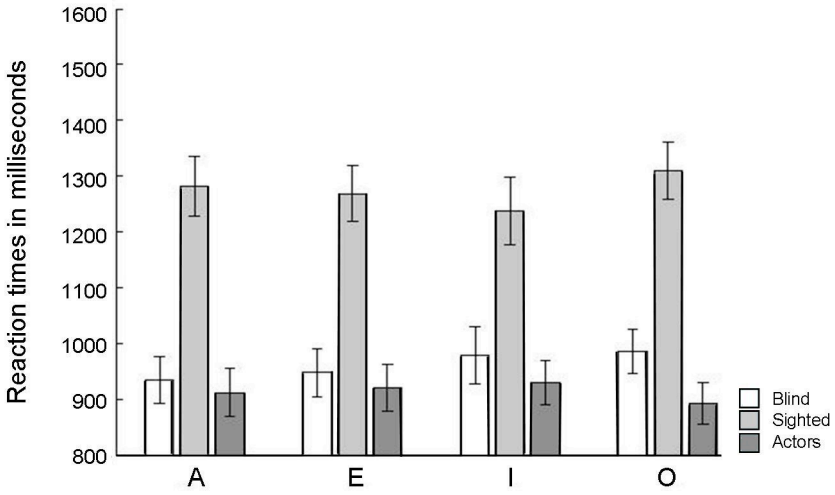

Figure A5. Reaction times in milliseconds in the vowel discrimination task. Reaction times are depicted for each vowel category and group separately. Error bars indicate standard error of the mean. There was a main effect of group in RT data ($F_{(2,27)}$=11.11, p<0.001). Actors and blind showed comparable behavioural performances ($t_{(18)}$=0.55, p<0.590) while actors and sighted differed significantly ($t_{(18)}$=3.48, p<0.003; Bonferroni corrected significance threshold p<0.025).

Erklärung nach § 9 Abs. 1, Nr. c der Promotionsordnung zur Doktorin/ zum Doktor der Philosophie oder der Naturwissenschaften des Fachbereichs Psychologie der Universität Hamburg vom 03. Februar 2004

Hiermit erkläre ich, dass die von mir vorgelegte Dissertation nicht Gegenstand eines anderen Prüfungsverfahrens gewesen ist.

Hamburg, den _____

Unterschrift

Eidesstattliche Erklärung nach § 9 Abs. 1, Nr. d der Promotionsordnung zur Doktorin/ zum Doktor der Philosophie oder der Naturwissenschaften des Fachbereichs Psychologie der Universität Hamburg vom 03. Februar 2004

Hiermit erkläre ich an Eides statt, dass ich die vorliegende Arbeit selbständig und ohne fremde Hilfe verfasst habe. Andere als die angegebenen Quellen und Hilfsmittel habe ich nicht benutzt und die wörtlich oder inhaltlich übernommenen Stellen als solche kenntlich gemacht.

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