Cortical processing of somatosensory information in people with blindness

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1   Introduction

Most research on the physiology of exteroceptive sensory systems was accomplished regarding the visual and auditory sensory systems as these are the dominant senses humans use for orientation and interaction. The relevance of particular senses, however, differs between individuals. While most humans mainly rely on their visual sense, people who are blind primarily depend on their auditory and tactile senses, for example for navigation, social interaction, or object recognition. Especially for communication with Braille, a coding system that uses tactile means in form of patterns of raised dots to encode letters, numbers, and punctuation (Braille, 1829), the sense of touch is of paramount importance for people who are blind.

Advancements in neuroscientific brain imaging techniques, such as electroencephalography (EEG), magnet resonance imaging (MRI), or transcranial magnetic stimulation (TMS), make it possible to noninvasively examine the neurophysiological substrates of sensory and memory processes (e.g., He et al., 2018; Schnitzler, 2000). These techniques also offer the opportunity to expand research on the effects of sensory deprivation beyond the behavioral level and allow a detailed examination of underlying cortical plasticity. While changes in the visual cortex in people with blindness have been studied extensively, cortical alterations in relevant brain areas for the remaining senses have received less attention. Studies on blindness-driven cortical plasticity in the somatosensory cortex are especially scarce (Voss, 2019).

This dissertation thus seeks to broaden existing knowledge on the cortical processing of tactile information and alterations in such processing that arise from vision loss, via a focus on somatosensory event-related potentials in individuals with and without blindness as measured by EEG.

The following chapters cover information on the visual and somatosensory system and neural plasticity following blindness. EEG and event-related potentials are described in the chapter on methodology. The objectives of this thesis are outlined in chapter five, the articles published in the course of this thesis bulild chapter six and seven, and future perspectives follow the overall conclusion in chapter eight.

2 The sensory systems of touch and vision

Just like other human sensory systems, the somatosensory and visual systems are hierarchically organized. They comprise an input sensor with different types of receptors transducing the physical stimuli into electric signals, a transmission path for the electrical signal from the sensor to the brain, and the information processing unit entailing thalamical nuclei that project to primary and secondary sensory cortices, which themselves forward the information to association areas ultimately forming the actual percepts (Dudel, 1986; Marques, 2011; Pinel & Pauli, 2007). Existing feedforward and feedbackward connections indicate a high degree of interactive and parallel processes in cortical areas relevant for sensory perception (Dijkerman & Haan, 2007; Pinel & Pauli, 2007; Tong, 2003). This chapter covers basic information on the somatosensory and visual system, in order to provide a brief introduction of these highly complex sensory systems that are of relevance for this thesis.

2.1 Somatosensory system

The human somatosensory system conveys different kinds of information: interoceptive information, e.g., about blood pressure and temperature, proprioceptive information, e.g., on limb position and muscle tone, and exteroceptive information covering thermic, nociceptive, and mechanical stimulations (Craig, 2002; Pinel & Pauli, 2007; Schandry, 2016; Schmidt, 1986a). As the present thesis examines the neurophysiology of fine discriminative touch using mechanical stimuli in the experimental design, this section's focus is on the processing of exteroceptive stimuli.

Four different types of mechanoreceptors responding to mechanical pressure or distortion form the basis for tactile perception on glabrous skin (Gardner & Martin, 2000; Johnson, 2001; Schmidt, 1986b). Slowly adapting afferents end in Merkel cells in the epidermis (SAI) or have Ruffini corpuscles located in the dermis as end-organs (SAII). Due to their structure and transducing features, both receptors mainly respond to slow or static stimulation or deformation of the skin. Rapidly adapting afferents end in a Pacinian corpuscle (RAII) in a deeper layer of the dermis, or in various Meissner corpuscles (RAI) in superficial layers close to the epidermis. The

receptive fields of Meissner's corpuscles only cover small surfaces receiving information with a high level of detail. As Meissner's corpuscles are highly concentrated in fingertips and lips, humans show maximum tactile sensitivity in these areas with high innervation density. Free nerve endings close to the skin surface also contribute to the detection of touch, but are primarily relevant for the perception of pain and temperature (Gardner & Martin, 2000).

Two ascending pathways convey somatosensory information to the somatosensory cortex (Pinel & Pauli, 2007; Schandry, 2016; M. Zimmermann, 1986): The anterolateral system is responsible for the processing of pain and temperature, while the posterior column-medial leminiscus pathway (Figure 1) conveys information about two-point discrimination, vibration, proprioception, and information of fine touch (Al-Chalabi et al., 2022). Tactile sensory input received at the fingers reaches the central nervous system via the ganglion spinale at the fifth, sixth, and seventh cervical vertebrae (i.e., dermatome C6, C7, and C8). Axons from first-order neurons in the ganglion spinale convey the information via the Fasciculus cuneatus as part of the posterior column to second-order neurons in the nucleus cuneatus in the medulla oblangata, where the axons decussate to the side contralateral to the initial stimulation. From there on, information ascends in the lemniscus medialis which synapses with third-order neurons located in the thalamic nucleus ventralis posterior. The thalamic nucleus projects mainly to the primary somatosensory cortex (SI), located in the gyrus postcentralis (Brodmann area (BA) 1, 2, 3a, 3b), and to a smaller degree to the secondary somatosensory cortex (SII), ventral and posterior to SI (BA 40, 43).

Illustrating the somatotopic organisation of SI, the sensory homunculus depicts which cortical area receives information of which body part (see Figure 1, section A). The larger the covered cortical area of a body part is the more sensory innvervations it has, indicating high somatosensory sensitivity in this body zone. Especially hands, lips, and face innervate disproportionally large areas in the somatosensory cortex. It has to be noted, however, that each of the four brain regions that are part of SI has a slightly different cortical representation of the contralateral body side (Kaas et al., 1979; Pinel & Pauli, 2007).

Figure 1

Posterior column-medial leminiscus
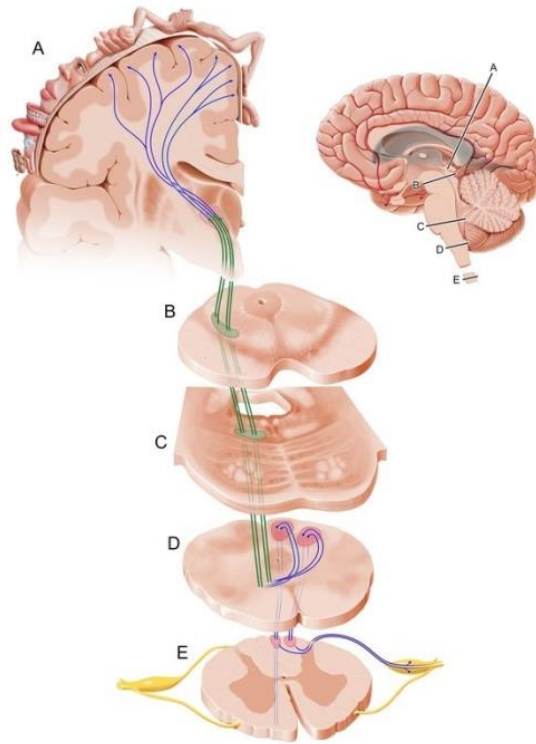
Note. Posterior column-medial leminiscus pathway that conveys information about fine discriminative touch, vibration, two-point discrimination, and proprioception form the spinal chord (E), via medulla oblangata (D), pons (C), and mesencephalon (B) to the somatosensory cortex in the postcentral gyrus (A) (Al-Chalabi et al., 2022). Captial letters A-D mark sections of the corresponding brain areas, E a section of a cervical part of the spinal chord. The sensory homunculus spreading across the somatosensory cortex is visible in section A. Adapted from © Kenhub (www.kenhub.com); Illustrator: Paul Kim.

The four areas of SI are cytoarchitectonically, connectionally, and physiologically distinct (Whitsel et al., 2019). BA 3b is often referred to as SI proper, given its density of cutaneous input and its structural similarities with other primary sensory cortices (Kaas, 1983; Martuzzi et al., 2014; Tabot, 2013). The main input of the thalamus ends up in BA 3b and travels from there posterior to BA 1 and BA 2. Also, the complexity of receptive fields and processed information seems to increase on an anterior–posterior axis supporting the assumption of a functional hierarchy in the

subregions of SI (Iwamura, 1998; Klingner et al., 2011; Kurth et al., 2000; Schellekens et al., 2021). BA 3a also receives thalamic input but, in contrast to BA 3b, rather concerning proprioception. Localized posterior to the motor areal BA 4, BA 3a is seen as transitional zone between motor and sensory areas and is, in view of its high connectivity with BA 4, functionally associated with the awareness and planning of movements (Gale et al., 2021; Kaas, 1983; Tabot, 2013; Zarzecki et al., 1978). Whereas SI mostly processes tactile information from the contralateral body side, SII primarily deals with information from both body sides, retrieving its main input from SI (Lamp et al., 2018; Pinel & Pauli, 2007; Ruben et al., 2001; M. Zimmermann, 1986). Receptive fields in SII are less fine-grained compared to SI and cover for example multiple digits (Bretas et al., 2020; Ruben et al., 2001). Both primary and secondary somatosensory cortices are connected to the posterior parietal cortex (BA 5, 7) contiguous to SI, an association area where the integration and interpretation of various kinds of sensory information take place. SII also sends information to the posterior insula, which is associated with sensomotoric functions, among others (Dijkerman & Haan, 2007; Klingner et al., 2011; Ruben et al., 2001; Uddin et al., 2017). The structure of SI and abutting areas BA 5 and BA 7 are shown in Figure 2.

Figure 2

The primary somatosensory cortex
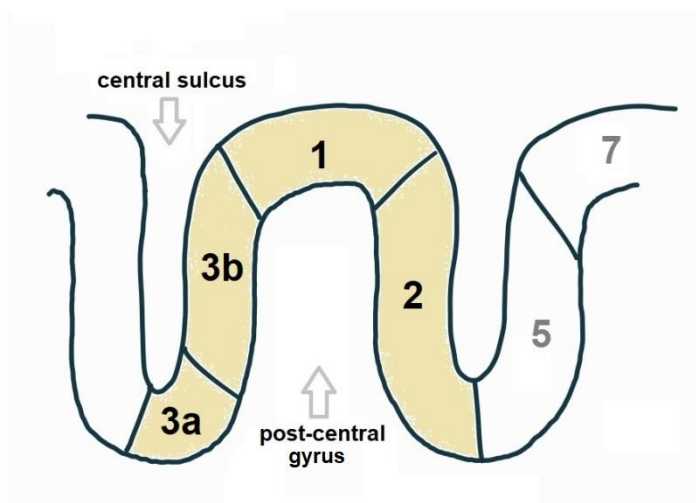
Note. The primary somatosensory cortex (SI) coloured in yellow, with its subregions BA 3a, 3b, 1, and 2, and the contigous areas of the posterior parietal cortex BA 5 and BA 7. Figure based on Tabot (2013).

2.2 Visual system

Inside the eye, the sense organ of the visual system, light reflected from the environment is transduced into neuronal signals. Light intensity and wavelength determine the perception of brightness and color (Pinel & Pauli, 2007). The light passes through the cornea and the pupil, is focused by the lense, and hits five different types of receptors in the different layers of the retina: rods and cones, horizontal cells, bipolar cells, amacrine cells, and ganglion cells (Marques, 2011; Pinel & Pauli, 2007; Remington & Goodwin, 2012). Rods and cones are photoreceptor cells containing photopigments that absorb photons of light. This absorption initiates a chemical cascade eventually leading to an increase or decrease in neurotransmitter release. While rods are activated in situations with dim lumination and are located everywhere in the retina except the fovea, cones have the highest density there, are active in well-lit conditions, and allow a sharp, colored perception (Pinel & Pauli, 2007; Remington & Goodwin, 2012). Bipolar cells create the link between photoreceptor cells and the ganglion cells as second order neurons. They are categorized in on/depolarizing cells that are activated with light and off/hyperpolarizing cells that are activated by darkness (Remington & Goodwin, 2012). Horizontal and amacrine cells are specialized in lateral communication between photoreceptors and between bipolar and ganglion cells, respectively (Pinel & Pauli, 2007; Remington & Goodwin, 2012).

Axons of the ganglion cells finally convert into the optic nerves that convey the electric signal via the chiasma opticum to the superior colliculus and the geniculate body of the thalamus, from where fibers of the optic tract (geniculocalcarine tract) project the signal to the primary visual cortex. Nasal fibers of each eye decussate and join the temporal fibers of the contralateral eye at the chiasma opticum, such that information from left and right visual fields is processed contralaterally in the primary visual cortex. The superior colliculus is primarily important for the control of saccadic eye movements and visual orientation (Remington & Goodwin, 2012). The lateral geniculate nuclei (LGN) consist of six different layers of magnocellular and parvocellular layers. While magnocellular layers (M layers) react in particular to movement, parvocellular layers (P layers) are more sensitive regarding color and texture (Remington & Goodwin, 2012). The visual pathway is illustrated in Figure 3, Panel A.

The primary visual cortex (V1; BA 17, also called the striate cortex) is located in the occipital lobe and is divided into a superior and inferior part by the calcarine sulcus (Pinel & Pauli, 2007; Remington & Goodwin, 2012). The majority of V1 is buried in the calcarine fissure. In V1, neurons with similar functional properties are grouped in columns (Remington & Goodwin, 2012). Hubel et al. (1977) suggested that those are themselves collected into assemblies, containing both types of ocular dominance columns, i.e., columns that process information either from the left or the right eye (Horton et al., 1990). The LGN and V1 have a retinotopic organization, meaning that adjacent points in the visual field are presented in adjacent points in the LGN and adjacent columns in V1, respectively (Remington & Goodwin, 2012). The areas surrounding V1 are often referred to as the extrastriate cortex (BA 18, 19) and contain multiple higher visual association areas, namely V2 to MT/V5 (see Figure 3, Panel B). V2 as the secondary visual cortex has the strongest feedforward and feedbackward connections to V1. Building on the information on low-level features forwarded from V1, more complex computations are performed in the visual association areas. Each visual area is associated with a specific type of function, such as motion processing, or form and color perception.

Typically, two pathways are described to connect V1 to extrastraite areas: the ventral and the dorsal stream. The former is believed to mainly process information about object shape and recognition, and travels along the ventral part of the brain to the inferior temporal lobe (V2, V4). The dorsal stream runs to the posterior parietal lobe (V2, MT/V5) and is assumed to be part of motion and spatial perception (Choi et al., 2020; Vanderah & Gould, 2021).

Figure 3

Visual pathway and visual cortex
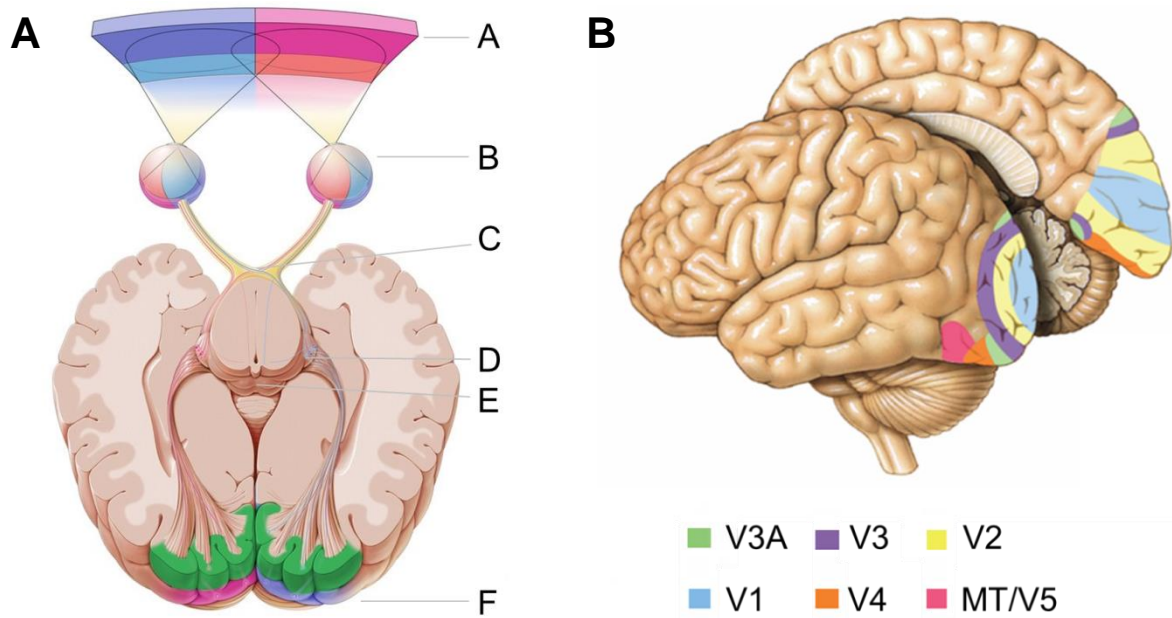
Note. Panel A: A - left (blue) and right (pink) visual field, B – eyes and reflection of the visual field parts on the retina, C – chiasma opticum, D – lateral geniculate nuclei (LGN) E – superior colliculus, F - visual cortex. Adapted from © Kenhub (www.kenhub.com); Illustrator: Paul Kim. Panel B: Visual corteces V1 to V5, MT = medial temporal area; adapted from Pinel (2011).

3   Blindness and neural plasticity

3.1 Visual impairment and blindness

Visual impairment and blindness arise due to disruption in the visual pathways described in the previous chapter. Depending on the cause of visual impairment or blindness, the disruption takes place at different stages and can occur before (seldom the case), during, or after the prenatal development of the visual pathways (Bock & Fine, 2014; World Health Organization, 2019). Independent from the location and onset of the disruption, the remaining functionality of the visual system can be measured in a standardized way. The ICD-10 assigns visual impairment and blindness to different categories, classified by visual acuity. The categories are displayed in Table 1. Categories zero to two concern visual impairment, while categories three to five comprise individuals with blindness, with a higher category corresponding to increasing impairment / blindness severity. Visual acuity scores refer to the results in the Snellen test, a routine test for eye sight, in which progressively smaller letters on a chart at (usually) six meters distance have to be read out. The resulting scores consist of two numbers, e.g., 6/18. The first number describes the distance at which the person taking the test is able to read the letters, the second number is the distance at which individuals with healthy eye sight are able to read the letter of the same size (Azzam & Ronquillo, 2022).

Table 1

Categories of visual impairment and blindness as defined in the ICD-10

ICD-10 category		Visual acuity (equal or better than)
0	No / mild visual impairment	6/18
1	Moderate visual impairment	6/60
2	Severe visual impairment	3/60
3	Blindness	1/60 or finger count in 1m distance
4	Blindness	light perception
5	Blindness	no light perception

Note. Adapted from *ICD-10-CM 2022*, 2021.

There are three different types of blindness, categorized according to onset. *Congenital blindness* refers to the condition in which no visual information reaches the brain at or within one month after birth. Two of the most frequent causes are retinopathy of prematurity (ROP) and optic nerve hypoplasia (Fine & Park, 2018; Solebo et al., 2017). The former describes the irregular development of the retinal blood vessels in preterm infants, presumably caused by factors related to an extremely low birth weight and short pregnancy, or as a side effect of oxygen therapy during neonatal intensive care (Karna et al., 2005; World Health Organization, 2019). Optic nerve hypoplasia refers to an underdeveloped optic nerve, which can be caused by genetic factors or environmental factors during pregnancy, such as toxin exposure (Tornqvist et al., 2002).

Next to congenital blindness, a further distinction is made between *early blindness* and *late blindness*, though the definitions differ between research groups. In the literature, the upper limit of the age range defining early blindness varies from an onset-age of 3 to 16 (e.g., Amedi et al., 2005; Cohen et al., 1999; Leporé et al., 2010; Postma et al., 2007; Sadato et al., 2002; Wan et al., 2010). An onset age after the age of 16 is generally considered as late blindness. Common causes for acquired blindness are cataract, glaucoma, age-related macular degeneration, diabetic retinopathy, ocular trauma, and infectious diseases (World Health Organization, 2019).

3.2 Neural plasticity following blindness

Neural plasticity describes the ability of the nervous system to modify itself in structure, functions, and connections in response to intrinsic or extrinsic stimuli (Cramer et al., 2011). In other words, the brain can reorganize itself as a reaction to both experience and injury (Bernhardi et al., 2017). The brain reacts to variable and persistent demands demonstrating in developmental, activity-dependent, learning-dependent, and injury-dependent neuronal plasticity (Bernhardi et al., 2017; Caroni et al., 2014; Mateos-Aparicio & Rodríguez-Moreno, 2019). Plasticity can be adaptive, i.e., with a gain in function (Cohen et al., 1997) or maladaptive, associated with negative consequences, i.e., a loss in function (Nudo, 2006). Involved biological processes comprise changes in neuronal excitability and neurotransmission, neurogenesis, formation and elimination of synapses, and axonal and dendritic

arborisation and sprouting (Bernhardi et al., 2017). Changes in transmission efficacy are usually followed by structural changes, maintaining a homeostatic balance and assuring the stability of neuronal circuits. That is, sustained high neuronal activity results in a decrease of synaptic connectivity while sustained low activity affects an increase (Fauth & Tetzlaff, 2016).

Blindness has been used as a model to study neuronal plasticity since the 1960s (Fine & Park, 2018; Pascual-Leone et al., 2005; Rauschecker, 1995; Voss et al., 2010). Indeed, the main focus of sensory deprivation research following the pioneering study by Wiesel and Hubel (1963), in which they compared the visual pathways of sighted and visually deprived kittens, has been on the visual system (Voss et al., 2008). Studies on blindness entail the advantage of relatively easily generated animal models as well as the opportunity to study both sensory and cognitive plasticity in humans (Fine & Park, 2018). Compensatory cortical changes arise due to cognitive and sensory adjustments, driven by loss of the visual sense, and by compensatory behaviors due to the need of interaction with the world without the possibility to rely on the visual sense.

Besides the level of blindness severity, the age of blindness onset affects the extent of neural plasticity. Although research has constantly shown that the brain reorganizes itself after vision loss at all ages, the degree of reorganization varies depending on the age of blindness onset (Fine & Park, 2018; Röder et al., 2021; Voss et al., 2008). Differences in the definitions of early blindness and the upper limit of the corresponding age range can be attributed to the varied interests of the researchers in processes affected by neural plasticity: vision loss in early years affects both sensory and cognitive development, whereas during adolescence sensory skills are already adult-like, and vision loss mainly affects the continuing development of cognitive processes (Daw, 2014; Sadato et al., 2002; A. Zimmermann et al., 2019). The literature describes a sensitive developmental phase up to the early teenage years, in which the extent of cortical reorganization is substantial, with alterations in neural function possibly occurring across more than 25% of the cortex (Fine & Park, 2018). Reorganization following vision loss at an older age, however, appears to take place to a minor degree (Collignon et al., 2013; Fine & Park, 2018; Hensch, 2005; Sadato et al., 2002). Congenital and early blind individuals thus usually show greater compensatory cortical reorganization as well as

enhanced abilities in their remaining senses, compared to late blind individuals (Ankeeta et al., 2021; Burton et al., 2002; Voss et al., 2008). However, there is evidence to suggest that this does not apply to all sensory and cognitive tasks.

In general, multiple behavioral advantages are assigned to individuals with blindness across a wide range of non-visual perceptual and cognitive tasks. For example, participants with blindness outperformed sighted controls in various aspects of linguistic processing, voice recognition, rhythm perception, numerical processing, and short- and long-term memory performance with different kinds of information, and showed altered attention (Amedi et al., 2003; Fine & Park, 2018; Föcker et al., 2012; Loiotile et al., 2020; Pang et al., 2020; Röder et al., 2007; Röder & Rösler, 2003; Voss et al., 2004; L. Zhang et al., 2019).

At the neurophysiological level, blindness effects neurotransmitter regulation and metabolic pathways, with a shift towards excitatory transmitters and a metabolic upregulation in the occipital cortex (Weaver et al., 2013). The synaptic microstructure is largely comparable to that of sighted individuals, especially with regards to the general retinotopic organization of the visual cortex, which appears to be developed independently from experience (Fine & Park, 2018). Visual experience thus is believed to sculpt and refine already existing formations and circuits (Fine & Park, 2018; Wiesel & Hubel, 1963). Blindness is further associated with decreased cortical folding and increased cortical thickness (Anurova et al., 2015). The latter seems to arise due to a reduction in both prenatal progenitor cells and postnatal pruning (Fine & Park, 2018). In most of the cases of congenital and early blindness, white matter traces in the visual system develop regularly during the second trimester of pregnancy, and start to atrophy after major parts have already been established (Shu et al., 2009).

A large body of work also describes the involvement of the visual cortex in non-visual processes, i.e., cross-modal plasticity in the visual cortex (e.g., Amedi et al., 2003; Ankeeta et al., 2021; Bedny, 2017; Borst & Gelder, 2019; Burton, 2003; Burton et al., 2002; Frasnelli et al., 2011; Gougoux et al., 2005; Jiang et al., 2016; Ptito et al., 2008; Sadato et al., 1998; Voss & Zatorre, 2012). The processing of cross-modal input in the visual cortex is facilitated by strengthened pre-existing pathways including several different nuclei of the thalamus and the superior colliculus (Voss,

2019). Occipital activity can be seen for example during tactile, auditory, or verbal tasks, and correlations have been reported between the magnitude of such activity and task performance. Studies using TMS revealed a causal association between activity in visual cortices and various non-visual tasks, evidenced by a decreased performance when occipital areas were temporarily inhibited by TMS-pulses (Amedi et al., 2004; Cohen et al., 1997; Collignon et al., 2007; Hamilton & Pascual-Leone, 1998; Ptito et al., 2008). Based on these findings, it has been suggested that brain areas are metamodal and constituted to perform a designated function or computation regardless of the sensory input modality (Pascual-Leone & Hamilton, 2001). Following this hypothesis, visual areas maintain their innate modular function after vision loss, and process information from the other senses to complete tasks similar to those sighted individuals typically perform with visual input (e.g., Collignon et al., 2011; Mattioni et al., 2020; Poirier et al., 2005; Ratan Murty et al., 2020; Ricciardi et al., 2007). This seems to be particularly true for higher-order areas that are anyway rather task-selective and sensory-independent (Amedi et al., 2017; Bell et al., 2019; Voss, 2019). Lending support for the metamodal hypothesis, research suggests alpha oscillations in the posterior occipital cortex (involved in visual expectancy in sighted individuals) subserve tactile anticipation in participants with early blindndess (Gurtubay-Antolin et al., 2023). Also, the visual word form area (VWFA) was reported to be active during Braille-reading (Burton et al., 2002). However, the supporting results might partly be a consequence of experimental bias and methodological issues (Fine & Park, 2018).

Some researchers assert that the occipital cortex in general is supramodal, which only becomes evident in the absence of visual input (Pascual-Leone & Hamilton, 2001). So far, however, research results on this topic are mixed (Fine & Park, 2018). The underlying mechanisms of cross-modal plasticity therefore remain unclear.

In addition to cross-modal plasticity, there is also evidence for blindness-driven intra-modal plasticity, meaning that vision loss also affects the functioning of the remaining intact sensory systems (Borst & Gelder, 2019; Mortazavi et al., 2022; Pascual-Leone & Torres, 1993). Depending on the task, some studies have found an enhancement of function in the sensory areas of the remaining senses, while others have found lower activity in these areas in combination with higher functional engagement of the occipital regions (Jafari & Malayeri, 2014; Sadato et al., 1998).

Thus, many questions regarding the effects of vision loss on tactile and auditory perception remain unanswered (Voss, 2019).

3.2.1 Tactile perception in blindness

There is a commonly held belief that individuals with blindness have superior tactile perception, and indeed anecdotal and experimental evidence supports such an association, for example in the perception of haptic properties and spatial acuity (Boven et al., 2000; Kumari et al., 2022; Sathian & Stilla, 2010; Voss, 2019; Wong et al., 2011). However, empirical data suggests that tactile superiority of individuals who are blind is evident only in some tactile tasks. It is assumed that people with blindness preliminary perform better in tasks which are practice-related, such as braille-reading, which necessitates fine discriminative touch and microspatial processing (Foulke & Warm, 1967; Grant et al., 2000; Kumari et al., 2022; Sathian & Stilla, 2010). It has also be shown that, compared to sighted individuals, those who are blind use a different spatial reference frame for tactile perception, as they mainly use anatomical coordinates to localize touch, while sighted individuals, after integration with posture, also use external space (Schubert et al., 2015).

It is not yet clear whether enhanced tactile abilities in the blind arise from the increased usage of the sense of touch for daily life activities (tactile experience hypothesis), and are therefore facilitated by blindness, or whether the sensory deprivation itself results in enhanced abilities in the remaining senses (visual deprivation hypothesis; Sathian & Stilla, 2010; Wong et al., 2011). Most likely, intra- and cross-modal plasticity can be seen as a result of the combination and interaction of both training and blindness-driven cortical reorganization independent from training (Voss, 2019). Consistent with this assumption, training can improve tactile abilities in (blindfolded) sighted participants and cross-modal activity comparable to that seen in participants with blindness has been reported after training sessions (Harris et al., 2001; Kauffman et al., 2002; Merabet et al., 2008; Postma et al., 2007). Also, inter-individual differences in the tactile abilities of people with blindness and the better task performance of individuals with blindness who are trained Braille-readers (compared to those who do not use Braille), reinforce the role of acquired tactile expertise as an external, environmental factor alongside cortical alterations and sensory enhancement solely caused by vision loss (Facchini &

Aglioti, 2003; Voss, 2019; Wong et al., 2011). Whereas occipital activation during tactile tasks has been reported to be enhanced in individuals with blindness compared to sighted controls (e.g., Amedi et al., 2010; Burton et al., 2002; Collignon et al., 2013; Frasnelli et al., 2011; Ptito et al., 2008), recruitment of other relevant cortical areas such as somatosensory cortices were comparable (Amedi et al., 2010; Bauer et al., 2015; Borst & Gelder, 2019; Burton et al., 2002; Sadato et al., 1998) or even lower (Sadato et al., 1998) in most studies.

It has to be noted, however, that research has predominantly focused on cross-modal rather than intra-modal plasticity, and the body of existing literature on information processing in the somatosensory cortex after vision loss is rather sparse (Voss, 2019). This thesis seeks to add to this topic by exploiting the advantages of EEG, allowing for real-time observation of cortical activity. Processes of interest were those involved in somatosensory memory maintenance (article 1) as well as those required for internal model formation, i.e., anticipatory and preparatory processes (article 2) in tactile tasks necessitating fine discriminative touch.

4 Methodology

4.1 Electroencephalography

Electroencephalography (EEG) is a method used to measure cortical voltage fluctuations. This can be achieved either with electrodes positioned in the area of interest inside the brain, or electrodes placed along the scalp. The latter, non-invasive method is typically used for medical routine diagnostics (e.g., of epilepsy or sleeping disorders), pharmacological treatment monitoring, and research on humans (Lutzenberger et al., 1985; Zschocke & Hansen, 2012). The electrical potentials measured on the scalp surface vary in amplitude and frequency and are the summation of excitatory postsynaptic potentials (EPSP) of synchronically active neurons oriented perpendicular to the scalp surface. Inhibitory postsynaptic potentials (IPSP) in neurons with similar spatial orientation also contribute to the summed field potential, but to a minor degree (Lutzenberger et al., 1985; Zschocke & Hansen, 2012). A major part of the potentials originates from apical dendrites emerging from pyramidal cells located in the fifth layer of the cortex. Those pyramidal cells have an axon that leaves the cortex and transports information to and from subcortical structures (Martin, 2021). Potentials directly emerging in subcortical structures, referred to as 'far-field' potentials, also contribute to the measured EEG signal (Zschocke & Hansen, 2012).

EEG is typically considered to have a poor spatial solution compared to metabolic-based brain imaging techniques (Burle et al., 2015). While there are various approaches to determine the sources in the brain generating the EEG signal (Awan et al., 2019), this neural source imaging problem is ill-posed in nature such that there is no unique solution. There are two principal mathematical solution techniques: parametric methods using all potential source locations, and non-parametric methods working with a predetermined amount of dipoles (Grech et al., 2008). For source localization in the course of this thesis, low-resolution electromagnetic tomography (LORETA) was used as a parametric solution technique. This is widely used and has been shown to deliver satisfactory results (Awan et al., 2019; Grech et al., 2008; Pascual-Marqui et al., 2002).

With EEG it is possible to measure both spontaneous cortical activity and brain activity during a specific event or task. The former gives information about general synchronized cortical activation and, for example, different states of consciousness, whereas the latter provides insight into the activity generated during task-specific computational operations (Luck, 2014; Zschocke & Hansen, 2012). Spontaneous activity is historically described in frequency bands differing in bandwidth and associated activation levels. The most prominent example is the alpha frequency band (8-12 Hz) that occurs in a relaxed waking state, with eyes closed, and during the transition into sleep (Lutzenberger et al., 1985).

4.1.1 Event-related potentials

Voltages that emerge time-locked to specific stimuli or events are called event-related potentials (ERP; Blackwood & Muir, 1990). The high temporal resolution is a great advantage of EEG, as it allows the continuous measurement of cortical processing from stimuli presentation to a following response (Luck, 2005). ERP thus enable the study of neurophysiological correlates of sensory and cognitive cortical processing (Sur & Sinha, 2009). To gain the ERP out of the EEG signal it is necessary to run many trials with the event of interest and then average the relevant epoch during electronic data pre-processing. With the assumptions that the brain shows comparable responses following the specific event in each trial, and noise and unrelated cortical activity is random throughout data collection, the averaging leaves the researcher with the event-specific cortical activity only, i.e., ERP.

ERP occur before, during or after a specific event (e.g., a stimulus, reaction, or psychological process) and consist of different components reflecting different aspects of the cortical processing. ERP are sensitive to both the extent and speed of neural processing and are commonly described with the parameters amplitude (in µV) and latency, which describes the time from stimulus onset till the maximal amplitude (Luck, 2014; Thomas et al., 2007). ERP components are often labelled with their polarity (P=positive; N=negative) and time of onset (e.g., P300). Negative potentials are associated with stimulated pyramidal cell clusters transmitting information to other cortical regions. A positive polarity correspondingly stands for inhibited or deactivated pyramidal cell clusters. As the EEG signal arises out of EPSP and IPSP that depend on neurotransmission, ERP can also be used in

research as an indirect reflection of neurotransmitter levels (Luck, 2014). Still a topic of debate is whether ERP emerge due to cortical activity additive to basic activity or due to phase-resetting of brain oscillations, or a combination of both (Cho et al., 2021; Min et al., 2007; Sauseng et al., 2007).

Researchers make a heuristic distinction between early or 'exogen' potentials with latency <100ms and late or 'endogen' potentials with latency >100ms. Exogenous potentials are evoked by events extrinsic to the nervous system and reflect the mere input processing (Donchin et al., 1978). They are influenced by physical features of the stimulus, like modality or intensity. Endogenous potentials are linked to psychological processes and are modulated by task-specific parameters and instructions (Blackwood & Muir, 1990; Donchin et al., 1978). A selective division is however not possible (Donchin, 1989).

Exogen evoked potentials play a particularly important role as diagnostic criteria in otological, ophthalmological, and neurological conditions. With auditory and visual evoked potentials (AEP and VEP) it is possible to quantify the functional integrity of the respective sensory system, providing valuable information about potential diseases. The same applies to somatosensory evoked potentials that are clinically used to detect and monitor functional impairment along the somatosensory pathway (Hegerl, 1998; Walsh et al., 2005). Alterations regarding amplitude or latency in ERP components linked to cognitive processing provide information about potential deficits and related neurological or psychiatric disorders. A prominent example is the P300, arguably the best-researched ERP component indexing working memory operations and salience processing, which is altered for example in dementia, schizophrenia, and addictive disorders (Hedges et al., 2016; Qiu et al., 2014; Sur & Sinha, 2009). ERP research aims to broaden existing knowledge on the functioning of sensory systems as well as on the (psycho-) pathology of disorders. Another objective is to find biomarkers that pave the way for preventive measures, can be used as objective measurements in treatment monitoring, or are valuable for (early) diagnostics.

Compared to other techniques and measurements, ERP are most suitable to directly study the cortical underpinnings of sensory and cognitive processing at the time of

their occurrence. Using this advantageous research method, this thesis' focus is on late somatosensory evoked potentials.

4.2 Overarching study design

Two research articles have been published within the framework of this cumulative dissertation. Both articles are based on the same study conducted at the Technische Universität Dresden. In course of this study, human participants with and without blindness performed a tactile task, while EEG was recorded. The study design encompassed a total of 12 different experimental conditions, all of which entailed the passive stimulation of participants' finger pads with different patterns of Braille pins. Each research article examines different sets of experimental conditions, each with a distinct focus of interest.

5 Objectives of the thesis

The intention of this thesis was to examine somatosensory cortical processing in modality-specific and supramodal brain regions in individuals with blindness. As described in the chapter on neural plasticity, the brain has the ability to adapt to a variety of events, including changes in the availability of exteroceptive information. We therefore compared ERP measured through EEG in individuals with and without blindness in order to identify potential group differences during somatosensory processing.

We focused on the higher-order cortical processing of somatosensory information, centering on psychological processes that take place beyond mere sensation. Our primary interest lay in investigating the processes involved in the anticipation and maintenance of tactile information. The first research article published as part of this thesis examines contralateral delay activity (CDA), an ERP component hitherto investigated primarily in the visual system, which is associated with short-term memory operations (Luria et al., 2016; Sur & Sinha, 2009; Vogel & Machizawa, 2004). The second article looks into contingent negative variation (CNV) as the primary outcome measure, an ERP component that is considered as a reflection of preparatory and anticipatory processes, that are also associated with internal model-formation (Loveless & Sanford, 1974; Naeije et al., 2016; Sherwell et al., 2017; Walter, 1964; Walter et al., 1964).

The purpose of this thesis was to gain insights on neurophysiological correlates of behavioural differences between individuals with and without blindness, specifically during a tactile task. By doing so, we first aimed to acquire a deeper understanding of somatosensory cortical processing in general, and changes in its functioning after vision loss and the subsequent increase in the alternative use of tactile information in particular. Secondly, this investigation on post-perceptual cortical processes holds value in a broader sense by providing valuable insights into the intricate mechanisms of cortical sensory processing and neural plasticity. Consequently, it has the potential to have meaningful implications for future research on sensory impairment and treatment options.

6   Article 1: What makes somatosensory short-term memory maintenance effective? An EEG study comparing contralateral delay activity between sighted participants and participants who are blind

This EEG study sought to provide further understanding of somatosensory memory processes, by measuring slow cortical negativity developing during short-term tactile memory maintenance (tactile contralateral delay activity, tCDA) in frontal and somatosensory areas. Features of tCDA, measured during a novel tactile change-detection task with varying loads of Braille pin patterns as stimuli, were compared between sighted participants and participants who are blind. During the task, auditory cues appearing at varying latencies between sample arrays could be used to reduce memory demands during maintenance. The present study details the neurophysiological underpinnings of superior performance in participants who are blind, adding to the compensation literature, while also using this expert-vs-novice contrast across wider analyses to ascribe functional relevance to neurophysiological findings related to somatosensory STM and the tCDA. Also, inferences about ultra-short term haptic memory are drawn based on the behavioural data.

Breitinger, E., Pokorny, L., Biermann, L., Jarczok, T. A., Dundon, N. M., Roessner, V., & Bender, S. (2022). What makes somatosensory short-term memory maintenance effective? An EEG study comparing contralateral delay activity between sighted participants and participants who are blind. NeuroImage, 259, 119407.

7 Article 2: Contingent negative variation to tactile stimuli – differences in anticipatory and preparatory processes between participants with and without blindness

Focusing on contingent negative variation (CNV) as a marker of anticipatory and preparatory processes prior to expected events, this EEG study investigated on a neurophysiological level whether people with blindness form top-down models of the world on short timescales more efficiently to guide goal-oriented behaviour. Participants with and without blindness completed a classic CNV task and a memory CNV task, both containing tactile stimuli to exploit the expertise of the former group. Behavioral differences (reaction times and percentage of correct responses, respectively) were investigated as well as whether differences in performance co-occurred with a distinct neurophysiological profile.

Breitinger, E., Dundon, N. M., Pokorny, L., Wunram, H. L., Roessner, V., & Bender, S. (2023). Contingent negative variation to tactile stimuli-differences in anticipatory and preparatory processes between participants with and without blindness. Cerebral Cortex, 33(12), 7582-7594.

8 Conclusion and future perspectives

This thesis contributes the field of cognitive psychophysiology, which focuses on finding physiological correlates of psychological processes, encompassing everything from mere sensation to the processing of perceived information (Rösler, 2011; Sommer, 2000). In this work, anticipatory, preparatory, and memory processes were of interest. The aim was to expand knowledge on the cortical processing of tactile information and alterations in such processing that result from vision loss. The sample completing the experimental tasks that required somatosensory perception and maintenance comprised sighted participants and participants with blindness that had extensive experience in reading Braille. The study design made it therefore possible to contrast novices with experts in terms of detailed somatosensory information processing. On the basis of this comparison, we gained new insights into both the general neurophysiological correlates of somatosensory cortical processing in tasks requiring fine discriminative touch, and neurophysiological changes accompanying blindness and the intense usage of the tactile sense. Both articles published in the course of this thesis focused on slow cortical potentials measured by EEG that were evoked by somatosensory stimuli.

The first article addressed tactile contralateral delay activity (tCDA) in frontal and somatosensory areas during short-term tactile memory maintenance. That CDA is present not only in visual but also somatosensory memory tasks was first reported by Katus et al. in 2015. The body of research on tCDA as an electrophysiological correlate of tactile STM is therefore comparatively small. tCDA specifically in participants with blindness has not yet been described. In our study, we found that participants who are blind showed higher tCDA amplitudes specifically over somatosensory areas. Somatosensory tCDA amplitudes correlated across the whole sample with behavioral performance and showed sensitivity to varying memory load, which additionally supports the site specificity of this component's functional relevance in STM maintenance. Differences between participants with and without blindness in the interplay between frontal and somatosensory areas during somatosensory maintenance also imply that efficient maintenance of complex tactile stimuli in STM is primarily facilitated by lateralized activity in the somatosensory

cortex. In a more general sense, the pattern of cortical activity in both groups further substantiated sensory recruitment models of sensory processing.

The second article's focus was on contingent negative variation (CNV) which is associated with anticipatory and preparatory processes prior to expected events. In contrast to (t)CDA, CNV is a well-studied ERP. However, CNV research with mainly or exclusively somatosensory stimuli is also scarce. Likewise, very few studies have addressed late cortical potentials in participants with blindness that are related to CNV, or constitute CNV itself. In our article on CNV, we report that participants who are blind reached higher performance rates in the memory task and showed greater late CNV amplitudes over central areas, while controls recruited more frontal areas. We therefore assigned enhanced stimulus expectancy and motor preparation to participants with blindness, which suggests that this group formed more robust task-relevant internal models that probably facilitated behavior in the experimental task requiring tactile perception.

Taken together, this thesis expands knowledge in psychology by contributing to the understanding of how sensory experiences can impact cognitive processes and by shedding light on the plasticity of the human brain. The results demonstrate that variations in memory performance between people with and without blindness are accompanied by disparities in associated event-related potentials and the topographic distribution of brain activity. Also, differences in neurophysiological preparatory processes could be implicated as part of the explanation for enhanced cognitive performance in people with blindness across different domains, as these processes are linked to internal model formation.

Our findings on somatosensory processing in participants with and without blindness contribute first to **fundamental research on exteroceptive sensory systems**, namely with

- support for sensory recruitment models
- support for relevance of event-related activity in sensory areas for memory performance
- support for the in general supramodal nature of CNV
- hints for modality specific CNV modulations.

Secondly, our findings contribute to research on **neural plasticity following blindness**, with

- evidence of intra-modal plasticity in people with blindness reflected in enhanced ERP (higher tCDA, higher lCNV) over somatosensory cortices
- enhanced performance on the behavioral level, associated with a distinct pattern of cortical activity
- further support that individuals with blindness show enhanced abilities in both sensory and higher-order cognitive processing (i.e., memory and internal-model formation).

Relevance of insights on cortical somatosensory processing

Research on the physiology of exteroceptive sensory systems contributes to the neuroscientific aim to understand operating modes, processes, and interactions in the human nervous system (Gage, 2015). The processing of sensory impressions, especially those received from the basic senses of vision, hearing, smell, taste, and touch, forms the basis for humans to perceive their surroundings. The senses can thus be seen as an interface between humans and their environment: Building on the mere sensation, the ability to choose, maintain, and integrate relevant sensory information allows humans to interact with their environment and one another (Goldman-Rakic, 1992). The focus on the tactile modality facilitates comparisons with existing literature on cortical underpinnings of psychological processes using sensory input from more extensively-studied modalities. The results provide additional evidence for fundamental physiological principles for anticipatory and memory processes that are shared across different sensory modalities (Bender et

al., 2010; Deecke et al., 1980; Dudel, 1986; Simson et al., 1977; Sreenivasan & D'Esposito, 2019).

A better comprehension of somatosensory processing and memory maintenance sheds light on the underlying cognitive processes of object recognition and sensorimotor learning (Gale et al., 2021; Gallace & Spence, 2009; Krakauer et al., 2019; Rincon-Gonzalez et al., 2011; Rossi et al., 2021). The development of preventive or curative measures to counteract impairments in this area, for example after stroke (Connell et al., 2008), would benefit from a broad knowledge base. Research on the neurophysiology of tactile perception is also fundamental for people who are blind, as a specification of cortical processes underlying (enhanced) tactile processing has the potential to improve assistive technologies that make use of the tactile sense, e.g., vibrotactile navigation tools (Elmannai & Elleithy, 2017; Mann et al., 2011). This might also enhance strategies to teach Braille in the long run (Mašić et al., 2020). Books, board games, and sheet music are available in Braille and technical devices such as Braille terminals make it possible for people with visual impairment to browse websites. Braille thus not only makes education accessible to people who are visually impaired or blind, but also enables them to take part in a wide range of social interactions (DBSV, 2022), which underlines the relevance of research in this context.

Relevance of insights on neural plasticity following blindness
Neural plasticity is a phenomenon found in the nervous systems of species from insects to humans. It is involved in brain development and homeostasis, learning and memory, sensorial training, and recovery from brain lesions (Bernhardi et al., 2017; Mateos-Aparicio & Rodríguez-Moreno, 2019). New insights in this area thus have the potential to stimulate research in a wide variety of fields. Consequently, studies on neural plasticity have been a major driving force in neuroscience research (Mateos-Aparicio & Rodríguez-Moreno, 2019).

The study of blindness-driven plasticity in particular, provides an opportunity to explore the influence of experience on the development and maintenance of neuroarchitecture and function (Fine & Park, 2018). Not only sensory plasticity can be examined but also cognitive plasticity in general, as a great amount of plasticity occurs due to the need for individuals with blindness to interact with the world with

their remaining senses (Fine & Park, 2018). Adding to fundamental knowledge on somatosensory processing, insights on how training and experience affect plasticity in the somatosensory system might also contribute to improve Braille teaching techniques. New findings regarding blindness-driven cortical plasticity may also facilitate the development of sensory substitution and restoration devices as well as rehabilitative and educational strategies (Mašić et al., 2020; Merabet et al., 2008). Furthermore, these insights might contribute to research on cortical adaptations after the loss of other sensory input beyond vision and facilitate the development of corresponding assistive technologies (Merabet et al., 2008).

Future perspectives

To get the most complete picture possible of neural changes occurring after vision loss and of how they affect somatosensory or other cortical processing, several unanswered questions need to be addressed. Information needs to be gathered regarding the time-sensitivity and experience-dependency of blindness-driven cortical plasticity. This could be done with further studies assessing the differences between individuals with diverse blindness etiologies, blindness severity, and onset. The identification of general differences in cortical adaptations following vision loss is of crucial relevance for treatment strategies. Research has shown that individuals with acquired blindness, whose visual system had developed normally, are more likely to benefit from sight restoration attempts, while individuals with congenital or early blindness find more success with sensory substitution devices, facilitated by the extent of pre-existing cross-modal cortical adaptations (Voss, 2019). From a sight restoration perspective, cross-modal alterations that enhance nonvisual processing might therefore be seen as maladaptive plasticity, which is worth prospective investigation (Heimler et al., 2014). Determining onset-dependent differences in plasticity and their implications for treatment strategies is particularly relevant for the aging global population, given that the majority of individuals affected with blindness were not born with it but acquired it late in life (World Health Organization, 2019). Identifying biomarkers that allow the prediction and monitoring of treatment responses in this context also has great potential (Cramer et al., 2011).

The effects of motivation and attention on neuronal plasticity need further investigation (Cramer et al., 2011), as do the ways in which plasticity shapes brain

morphology and physiology (Mateos-Aparicio & Rodríguez-Moreno, 2019). The underlying organizational principles of cross-modal plasticity are yet to be determined. However, given the large amount of research that already exists on cross-modal plasticity, it might be beneficial to place an additional focus on intra-modal plasticity and intensify research efforts regarding somatosensory and auditory processing in individuals with blindness. Subsequent studies in this context might also profit from advanced methods of analysis, such as multivoxel pattern activation (MVPA), which enable the examination of neural representations at a finer scale. Overlooked differences between individuals with and without blindness might then be uncovered (Fine & Park, 2018). Similarly, computational models relating altered brain activity to perceptional improvements in the auditory and tactile senses could advance the field dramatically (Fine & Park, 2018). Another branch of study could further examine the cause for superior behavioral performance of people with blindness, as it is still unclear whether sensory deprivation is the driving cause of this improvement, or whether it only accelerates the effects of training (Voss, 2019).

Furthermore, the investigation of potential biomarkers and neuronal plasticity in the context of mental disorders shows significant promise. As attentional processes needed for memory, anticipation, and motor preparation are also altered in various mental disorders, such as attention deficit hyperactivity disorder (ADHD), depression, anxiety disorders, autism spectrum disorder, schizophrenia or tic disorder, the ERPs under investigation in this thesis are also used in clinical psychology research (Bostanov et al., 2012; Morand-Beaulieu & Lavoie, 2019; Osborne et al., 2020; Prillinger et al., 2022; Ye et al., 2023; Yuan et al., 2020; D. Zhang et al., 2020). It would be intruiging in the future for example to investigate CNV and tCDA as markes of cognitive (dys-)function in patient samples during tasks involving tactile input. This investigation could shed light on potential differences in how cognitive processes are affected by mental disorders across different domains. Moreover, evidence-based interventions that link psychophysiological deficits associated with mental disorders (e.g., attention, information processing) with specific functional impairments, might foster the creation of treatment strategies that are more effective and tailored to individual needs (Hoagwood & Olin, 2002). The use of brain stimulation techniques harnessing neuronal plasticity is a promising

approach to reduce psychiatric symptoms. The scope of this approach has been and will continue to be expanded with new (non-invasive) technologies.

This dissertation adds to existing fundamental research on cortical sensory processing and neural plasticity. Given the growing body of knowledge concerning these topics, a key challenge that has to be addressed is the <u>translation of theoretical knowledge into practical applications</u> in the medical and psychological context. So far, non-invasive brain stimulation such as TMS and neuro-pharmacological therapies were identified as especially promising interventions to drive neural plasticity (Cramer et al., 2011). Therefore, the appliability and utility of these interventions in the context of sensory substitution measures, such as training of remaining senses, could be a focus of interest for research in the future.

9 Declaration of contributions to publications

Article 1:

Breitinger, E., Pokorny, L., Biermann, L., Jarczok, T. A., Dundon, N. M., Roessner, V., & Bender, S. (2022). What makes somatosensory short-term memory maintenance effective? An EEG study comparing contralateral delay activity between sighted participants and participants who are blind. *NeuroImage*, *259*, 119407.

Eva Breitinger (first and corresponding author) was responsible for formal analysis, data curation, validation, visualization, methodology. She also wrote the original draft of the manuscript.

Article 2:

Breitinger, E, Dundon, N. M., Pokorny, L., Wunram, H. L., Roessner, V., Bender, S. (2023). Contingent negative variation to tactile stimuli - differences in anticipatory and preparatory processes between participants with and without blindness. *Cerebral Cortex*, bhad062.

Eva Breitinger (first and corresponding author) was responsible for formal analysis, data curation, validation, visualization, methodology. She also wrote the original draft of the manuscript.

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