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Scheller, Meike

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Development of audio-haptic multisensory integration in sighted and non-sighted individuals

Meike Scheller

A thesis submitted for the degree of Doctor of Philosophy

University of Bath

Department of Psychology

September 2019

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Abstract

Our brain integrates sensory information from multiple senses in order to increase perceptual precision and accuracy. However, this process continuously develops throughout childhood and only reaches adult-like precision gains in late childhood or adolescence. Furthermore, recent research suggests that early sensory experience crossmodally influences perceptual processes in the other senses. For example, the absence of vision in early-blind individuals leads to a decreased accuracy in auditory space representation. At the same time, an increased use of the remaining senses, such as touch and hearing, has been shown to lead to perceptual enhancements in these senses. However, it is not known what role sensory experience plays for the development of multisensory integration. Combining behavioural and electrophysiological measures, this thesis investigates the development of audio-haptic integration in typically sighted individuals and individuals with different degrees of developmental visual experience: early blindness, late blindness, and low vision. Findings demonstrate that optimal audiohaptic integration develops between 13-17 years of age in sighted individuals. Furthermore, results suggest that early visual experience is not necessary for the development of this process, but rather delays it. In fact, early blindness leads to alterations in neural processing of audio-haptic integration that reflects a change integration strategy, indicated by a shift from sensory enhancement to sensory inhibition. Furthermore, late-onset blindness leads to an impairment in audio-haptic integration, which is reflected by changes in sensory and perceptual processing. The investigations presented here offer a new perspective on our understanding of perceptual development by recognizing the role of the sensory environment of the developing individual. The present findings highlight the importance of sensory consistency across development, pointing towards a central role of adolescent neural plasticity that can critically affect higher-order multisensory processes later in life. Furthermore, they offer important implications for the development and improvement of sensory rehabilitation approaches for the visually impaired.

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One of the biggest tasks that our brain has to master is to reduce the vast amount of information about the world around us and converge it into a single, coherent percept. Thereby, the brain does not only face the challenge of selecting and combining complex sensory information into coherent features, but it needs to do so in a sensible way that reduces the amount of uncertainty and ambiguity of the incoming information. For example, when trying to cross a busy street one needs to be able to perceive oncoming traffic and to predict its next state of movement in order to avoid collision. Even localizing the nearest vehicle requires our visual system to combine several sensory cues, such as size, occlusion, perspective, binocular disparity, or relative motion, to assess depth and to estimate the distance of the vehicle relative to us. Furthermore, we need to know about the position, configuration and orientation of our neck and eye muscles in order to estimate its location correctly. Unsurprisingly, combining several different cues, even within one sense, is not a trivial task. However, this rich pool of sensory information offers a crucial advantage to our brains – sensory redundancy. Sensory redundancy indicates that the same object features can be assessed through multiple cues. For example, an object's size can be both seen and felt at the same time thus increasing precision when, for example, discriminating between two objects. Also, an object's size can be assessed by listening to the sound it makes upon collision, such as hearing a large or a small ball bounce will result in different auditory characteristics (i.e. differences in amplitude and pitch). Notably, the ability of our brain to sensibly combine this redundant information allows us to interact with our environment in a meaningful way (Ernst & Banks, 2002; Rohde, van Dam, & Ernst, 2016). However, how does the brain develop the ability to combine information 'sensibly'? Given that the environment we are born into bears a high degree of variation and uncertainty, our brains have evolved to be more flexible (plastic) at birth, allowing us to adapt to the different demands of the specific environment (Kleim & Jones, 2008; Snell-Rood, 2013; Stein & Rowland, 2011).

Early sensory experience plays a key role in perceptual learning (Bahrick & Lickliter, 2004; Lewkowicz, 2014; Wallace & Stein, 2007). It allows us to associate, and ultimately make inferences, about the relationships between different features in the world. For example, within the first months of life, infants tend to associate features that share intersensory correspondence, such as those occurring in synchrony and in the same location (Lewkowicz, 2010). Infants' attention is quickly captured by objects that have high temporal and spatial synchrony, such as the sight and sound of a ball bouncing on the floor, or the sight and feeling of their own hand moving in space. In fact, intersensory redundancy is one of the main processes that scaffolds the development of our perception (Bahrick & Lickliter, 2000, 2012). However, while the availability

of multisensory information early in life is important for learning about characteristics of the environment, the brain does not yet exploit the full potential of redundant information at this stage. That is, while adults are able to reduce sensory uncertainty by integrating sensory information, young children are not (Ernst, 2008; Gori, Del Viva, Sandini, & Burr, 2008b; Nardini, Jones, Bedford, & Braddick, 2008; Petrini, Remark, Smith, & Nardini, 2014). This reduction in sensory uncertainty leads to the final, integrated percept to be more accurate and reliable than could be predicted by the best sense for a given task. For example, while visual information is typically more reliable than auditory information when assessing the size of a bouncing ball, combining both senses provides an even more precise perceptual estimate. The brain achieves this by weighting the visual information (in this example) more strongly than the auditory information when integrating them into one coherent percept. Importantly, there is not one sense that is more reliable for every single task, but some senses are more reliable for certain tasks than others (Gori, 2015; Macaluso et al., 2016). The way in which the adult brain integrates sensory information can be well-explained by the Bayesian optimal observer model, which is modelled by Maximum-Likelihood Estimation (MLE) and will be introduced in more depth in Chapter 1. In children, in contrast, the more robust sense for a certain task appears to dominate the final percept (Gori et al., 2008b; Petrini et al., 2014). One example, which will also be used throughout this thesis, is the use of auditory, visual and haptic (touch) information for assessing object size. While size can be assessed through any of these modalities, touch yields the most direct and unbiased estimate of three-dimensional object size. This can be attributed to the hand providing an independent size reference, against which other objects can be compared (Linkenauger et al., 2014). Furthermore, touch involves both tactile and proprioceptive information in parallel which provide a more robust estimate (Bresciani, Drewing, & Ernst, 2008; Rincon-Gonzalez, Naufel, Santos, & Helms Tillery, 2012). The visual assessment of object size, on the other hand, despite providing the highest spatial resolution (higher reliability), is more strongly dependent on visual perspective and distance and thus is less robust. Throughout development, the individual gains increasing sensory experience within and across the senses, allowing them to learn the statistical relationship of different feature-relations, for example that visual size can indicate either distance or actual object size, or that objects that look bigger tend to feel heavier. Furthermore, maturational changes in the processing substrate allow the developing individual to use sensory information more efficiently. For example, it has been shown that certain visual processing areas that allow the individual to combine two visual cues into depth information only mature in late childhood (Dekker et al., 2015). Both, sensory experience as well as maturation can explain why in children touch dominates the perception of object size and why later in development, haptic dominance transitions into a reliability weighted averaging of sensory input, with vision being more reliable (Ernst & Banks, 2002; Gori et al., 2008). However, it is still unclear what role sensory experience plays during the development of optimal multisensory integration.

One of the best and most direct ways of assessing what role sensory input plays for the developing brain, and how it affects perception, is by investigating the differences in multisensory processing between sensory impaired individuals and those with typical sensory input. In this thesis, I will focus on the role of visual experience for the development of non-visual multisensory integration, and how understanding this process will allow us to devise more efficient sensory rehabilitation strategies for individuals with visual impairment. In this case, visual impairment is employed as a model for sensory integration. Given that multisensory integration development is explored in terms of sensory reliability and sensory robustness, these findings could therefore also be relevant for other forms of sensory, or perhaps even motor, impairment. Based on the previously described example, object size perception, I will present three experimental studies that assess audio-haptic integration in sighted and visually impaired/blind children and adults. These will further be preceded by a literature review.

Chapter 1 provides a comprehensive overview of the conceptual background to the thesis, the applicability of its findings, and the current the state of the field by presenting a literature review on unisensory and multisensory perception, as well as the development of multisensory perception and its role for sensory rehabilitation through interactive technologies.

Chapter 2 is the first experimental study and assesses the neural basis of haptic dominance in sighted children aged 5-7 years. As haptic dominance has been demonstrated repeatedly using behavioural measures (Gori et al., 2008; Petrini et al., 2014), and so far no other study has assessed the neural signature of multisensory perception using audition and active touch, this study's contribution to my thesis is twofold. Firstly, on the conceptual level, it will provide evidence for the neural processes that govern haptic dominance in typically developing individuals, indexing developmental differences in the way sensory information is used. Secondly, this study provides a proof of concept for measuring neural markers of multisensory processing using active touch. This allows us to ensure that our size discrimination methodology, using audition and active touch, can be reliably used to assess both behavioural as well as neural markers of the same process. Crucially, by combining research from both the neural processes and resultant behavioural outcomes, we can gain a more complete understanding of multisensory integration (i.e., the mechanisms governing this process and its functional adaptiveness) under conditions of typical and atypical sensory experience (Krakauer, Ghazanfar, Gomez-Marin, MacIver, & Poeppel, 2017).

Chapter 3 comprises a behavioural study that investigates the role of visual experience on nonvisual (audio-haptic) multisensory integration. In this study, I first assessed the development of multisensory integration across the age range of 7-70 years in a group of 46 sighted children and 46 sighted adults, using an adapted version of the audio-haptic size discrimination task used by Petrini et al. (2014). Integration performance is quantified and compared across the age range using the Bayesian Ideal Observer model. This allows us to understand how multisensory integration of non-visual information develops in the presence of typical vision. Furthermore, I tested a group of 12 visually impaired adults and 15 visually impaired children with different levels of vision and onsets of vision loss. By comparing between individuals with early and late vision loss, and those with some residual vision, we are able to assess the impact of the presence and quality of developmental vision on multisensory integration.

Chapter 4 provides an investigation of the neural basis of multisensory integration in sighted and non-sighted individuals. As similarities and differences in behavioural performance between sighted and non-sighted individuals can be achieved by either the same or different neural mechanisms, this study tested typically sighted, early-blind and late-blind adults on the audio-haptic size discrimination task, in combination with measuring electrophysiological event-related potentials. Furthermore, I tested a group of typically sighted adolescents to assess whether differences in neural perceptual processing between sighted and blind adults can be explained by developmental maturation or sensory experience during development.

Lastly, I will provide a brief general discussion of the main research findings presented in this thesis and their contribution to our understanding of multisensory perception in the developing individual.

Chapter 1 and Chapter 2 have been published in *The Steven's Handbook of Experimental Psychology and Cognitive Neuroscience* and in *Brain Research*. Preliminary results of Chapter 3 have been presented at two international conferences (European Conference of Visual Perception 2017 and International Multisensory Research Forum 2018). The final results of Chapter 3 are currently under review. Chapter 4 will be submitted to a specialist journal in early 2020.

Chapter 1: Scheller, M., Petrini, K. and Proulx, M. J. (2019). *Perception and Interactive Technology*. In Stevens' Handbook of Experimental Psychology and Cognitive Neuroscience, J. T. Wixted (Ed.). doi:10.1002/9781119170174.epcn215

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Chapter 3: Scheller, M., Proulx, M.J. and Petrini, K. (2018): Audio-haptic cue integration across the lifespan. Presented at the *International Multisensory Research Forum* 2018, Toronto, Canada. Scheller, M., Proulx, M.J. and Petrini, K. (2018): Development of non-visual multisensory integration in sighted and non-sighted individuals. Presented at the *European Conference of Visual Perception* 2017, Berlin, Germany.

Chapter 1: Perception and Interactive Technology

Chapter 1 Introduction

This chapter introduces the literature and perspectives regarding our understanding of how the brain processes information to generate perception. It starts by describing how the brain integrates redundant information across the senses to disambiguate environmental stimuli and to enhance the quality of the final percept. Thereby, it introduces the Bayesian Optimal Observer model as a means to describing the integration process. This model has been frequently adopted to reliably describe and predict perceptual performance in psychophysical experiments (see Rohde et al., 2016). This chapter will further highlight the important role that development plays for the perceptual process, and how sensory- or motor-impairments at different stages in life affect perception in different ways. It will thereby provide the theoretical and conceptual background upon which the experimental studies are built. The second part of this chapter discusses the applicability of the findings of this thesis. Here, I introduce recent rehabilitation approaches to visual impairment that are based on interactive technologies using different approaches. That is, sensory rehabilitation distinguishes between the restoration and the substitution of a sense. While hearing restoration via cochlear implants has been largely successfully established to treat deafness early in life, there is less consensus about suitable restoration methods for the blind. In fact, sensory substitution might be more beneficial for an individual who lost their vision early in life, while the restoration of vision might be more useful for late-blind individuals. However, such recommendations cannot be made without taking the individual's development into account. The latter will be a central focus in the following chapters. I will further discuss what factors are currently limiting the advancement of rehabilitation strategies that arise from either the technological or bio-psychological domains. The chapter closes with a set of open questions that are addressed in the following chapters to allow us to advance our understanding of how interactive technologies can be used aid human perception.

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Statement from Candidate	Statement rom CandidateThis paper reports on original research I conducted during the period of my Higher Degree by Research candidature.				
Signed	M.Scheller	Date	09.09.2019		

Perception and Interactive Technology

Meike Scheller, Karin Petrini, & Michael J. Proulx*

* Corresponding author

Address: Department of Psychology, University of Bath, BA2 7AY, UK Telephone: +44 1225 385963 E-mail: m.j.proulx@bath.ac.uk

Abstract

"What does it mean, to see?" was the question that David Marr used to motivate his computational approach to understanding vision (Marr, 1982). Marr's answer, building on Aristotle, was that "vision is the process of discovering from images what is present in the world, and where it is" (p. 3). Although we humans might have a preference for visual perception, we are endowed with other senses that provide us with a rich experience (Spence, 2018). Therefore, the broader question might be: What does it mean, to perceive? Although this might be seen as a philosophical question of sorts, it gets to the important issue of how we define perceptual experience scientifically so that we may study it. The importance of defining it is crucial for research applications: If we aim to restore a sense such as vision in blindness or hearing in deafness, what does it mean to see or to hear such that we will know when restoration has been successful? This chapter reviews the interaction between multisensory perception and interactive technological approaches to sensory rehabilitation.

Although we humans might have a preference for visual perception, we are endowed with other senses that provide us with a rich experience (Bartoshuk, 2018; Goodman & Bensmaia, 2018; Mainland, 2018; McDermott, 2018; Spence, 2018). Therefore the broader question might be: What does it mean, to perceive? Although this might be seen as a philosophical question of sorts, it gets to the important issue of how we define perceptual experience scientifically so that we may study it. The importance of defining it is crucial for research applications: If we aim to restore a sense such as vision in blindness or hearing in deafness, what does it mean to see or to hear such that we will know when restoration has been successful?

This chapter reviews the interaction between multisensory perception and interactive technological approaches to sensory rehabilitation. It builds upon research in multisensory perception, sensory impairment, and the development of cognition to provide a foundation for understanding the psychological and neural basis for sensory rehabilitation. The interface between experimental psychology and technology provides challenges for basic and applied research, and, as a result, great opportunities to explore psychology and cognitive neuroscience in novel ways. We will first provide an outline of human sensory perception using single (unisensory) and multiple (multisensory) senses. This section highlights the interplay between different sensory modalities for the construction of a precise and accurate representation of the environment and the mechanisms our brains have developed to deal with physical uncertainty. Thereby, we specifically focus on optimal multisensory integration and its development during ontogeny. We then look into the adaptation of human perception to sensory or motor deficits, i.e. when one or multiple senses are impaired, or the motor system is not functioning normally. We describe how sensory loss/impairment impacts individuals in their everyday life and how deficits in one sense affect development of the remaining, intact senses. Also, the role that action and motor impairment play in the perceptual framework is discussed. We then outline current sensory rehabilitation techniques, with focus on auditory and visual rehabilitation, as these domains are more extensively investigated, thereby drawing a clear distinction between sensory restoration and sensory substitution. Their function and benefits of these different techniques for certain populations will be discussed and the chapter closes with some remarks on the outlook of interactive technology in sensory rehabilitation research and application.

Unisensory and multisensory perception

Our sensory systems have been shaped by evolutionary processes in such a way, that we are well-adapted to the natural world we live in and respond accurately to biologically relevant events (Kaas, 1989; Machens, Gollisch, Kolesnikova, & Herz, 2005; Nummela et al., 2013). Our sensory systems consist of arrays of different types of receptors: electromagnetic receptors, mechanoreceptors, chemoreceptors, thermoreceptors and pain receptors. We take up information from the environment using these receptors by transforming the different forms of energy (e.g. electromagnetic radiation, pressure waves) into electrical signals. This process is called transduction and enables us to perceive the different forms of stimuli in one and the same entity, namely in electrical impulses. These impulses, in turn, get sent to the central nervous system via neural pathways. Our central nervous system then processes and combines the information in a way that makes us perceive and recognize the world around us, eventually leading to ecologically relevant behaviour. The process of perception is strongly characterized by the combination of different, as well as redundant information, derived from our sensory organs. It is not a unidirectional process but stays in constant dynamic interaction with the actions we make. We actively use our body to facilitate perception by sampling our environment in the best way possible. For example, we need to actively explore or manipulate an object in order to gain enough information to recognise it (Goodman & Bensmaia, 2018; Hollins & Risner, 2000). This clearly makes touch an inherently active sense. However, with the aim of controlling our actions appropriately, perception must be frequently updated via sensory feedback, which arises from our actions. In fact, not only touch but also other senses like vision, proprioception and audition critically depend on the fine-tuned re-calibration of action and perception (Cressman & Henriques, 2011; Proulx et al., 2015).

The environment we live in is not stable but complex and dynamic. Moreover, all stimuli in our environment can be differentiated into multiple features. For example, sounds vary in amplitude and pitch while light varies in hue, luminance and colour. This vast variation of environmental stimuli that, on the one hand, supports our brain in structuring our complex lives, also emphasizes the necessity of our sensory systems to be quite flexible in the way they process incoming information – regardless of whether they arise from the same or from different modalities (Spence, 2018). Here is an example: in order to judge visually the spatial distance of an object, our eyes provide us with a number of different

visual cues. The perception of depth, which is crucial for estimating the distance and relative position of objects in space, arises from the combination of information from monocular cues like perspective, occlusion, shading, or relative size as well as binocular cues like retinal disparity and convergence. Furthermore, extra-retinal cues like signals from the eye muscles have also to be taken into account by the brain to determine in which direction the eyes are looking. This already shows that vision is much more complex than we often think and that even within one sensory system the amount of information our brain processes in order to compute a single visual feature – like depth – is immense and not restricted to the visual sense alone.

When we stick to the example of depth as a distance cue, we find that vision is the sense that is predominantly used for estimating spatial depth at distances that are out of physical reach (Battaglia, Jacobs, & Aslin, 2003). However our sense of hearing can additionally extract spatial distance cues from our environment using frequency spectrum, interaural loudness difference and interaural time difference (Moore, 2003). This gets particularly important when information in the environment is limited or ambiguous. Vision itself, for instance, is often ambiguous due to projection of a three-dimensional visual scene onto a two-dimensional retinal image. Mapping the two-dimensional image back into a threedimensional scene can result in many different possible outcomes. Similarly, reliance on self-motion can result in well-known perceptual misinterpretations, as the somatogravic illusion shows (see Figure 1). Here, the vestibular system, which provides rotational and translational movement cues, is tricked in a way that acceleration or deceleration of the body evoke the sensation of the own body facing upwards or downwards, which is in turn misperceived as an upward or downward tilting of the aeroplane. Correction of this interpretation can result in dangerous manoeuvres. Therefore, experience and use of additional sensory information are crucial. This shows that, if these ambiguous stimuli were processed by only one modality, the information they convey would remain ambiguous and perception would be less reliable. Also in other circumstances where one sensory modality is unavailable, other senses can compensate for the lack of it. For example. when navigating in complete darkness touch, hearing or selfmotion/interoception can compensate for lacking visual information (Tcheang et al., 2011; Petrini et al., 2015).



Figure 1: The somatographic illusion, which is frequently encountered in aviation, is an illusion by which the brain confuses high acceleration or deceleration with forward or backward tilting. It results from the ambiguous information arising from a displacement of the otolithic membrane above the excitable hair cells in the otolithic organs of the vestibular system (right column). In situations where the body is not accelerating or deccelerating (A, B), gravity is the only force acting upon the state of the hair cells and can be used to interpret the position of the head relative to the ground. (C) During fast changes of movement, on the other hand, acceleration forces lead to a displacement of the otolithic membrane and result in a bending of the hair cells, similar to the bending of the cells during tilt. As the brain uses information from the bending of hair cells to compute the head's position in space and relative to the ground, head tilt and translational movement can both lead to the same perceptual interpretation. Translational acceleration shifts the membrane in the same direction as an upward head tilt, whereas translational deceleration results in a similar response to a downward tilt. Visual information helps disambiguating this perceptual illusion. Reprinted with permission from Scheller, Petrini, & Proulx (2018).

Besides situations in which the information from one sense is ambiguous or missing, the presence of environmental or internal sensory noise drastically affects our perception. Noise relates to the perceptual uncertainty of sensory cue estimates. That is, the less certain we are about the accuracy of a certain perceptual estimate, the noisier it is. Notably, noise is present in all information that reaches our sensory organs. It arises from the physical nature of the stimulus, such as clutter affecting sound waves or quantum fluctuations of light. Also, system-internal noise, which results from neural coding of sensory information can affect perception at many different stages of processing. For example, even during tasks that appear easy at first, such as walking a straight line, the accumulation of sensory noise can become evident when only one sense is used at a time. Souman and colleagues (2009) showed that humans have difficulties maintaining a straight walking route when navigating without visual information. The authors blindfolded their participants and asked them to walk in a straight line for 50 minutes in a large, even field. Without the availability of visual reference points, participants quickly started walking in circles, often even over very short distances (with diameters < 20m; Souman, Frissen, Sreenivasa, & Ernst, 2009). These patterns in walking direction were even observed when participants were not blindfolded, but when navigational landmarks (e.g. sun, prominent geographical information) were unavailable. The authors concluded that when limiting high-resolution visual information or visual reference points, the remaining sensory systems used for navigation (proprioceptive and vestibular system) accumulate noise. That is, while the vestibular system provides information on rotation rate during walking, sensory noise in the perceived rotation rate becomes integrated and accumulates over time, leading individuals to veer from a straight path and eventually walk in circles.

Multisensory integration

Given that sensory information is typically ambiguous and noisy, how does the brain create an accurate and precise internal representation of the world that allows us to interact with it meaningfully? One way in which it achieves this is by synergistically combining redundant sensory information in a statistically optimal fashion (Ernst & Banks, 2002; Spence, 2018). For example, when estimating an object's shape we can use both visual and haptic cues, as both convey information about this physical property. When experienced simultaneously, the brain integrates this shape information across the

two senses by weighting each sensory cue by its reliability (the relative precision of the two cues; Ernst & Banks, 2002; Ernst & Bülthoff, 2004; Helbig & Ernst, 2007; Knill, 2007; Rohde, van Dam, & Ernst, 2016; see Figure 2). Thereby, "statistical optimality" refers to the reduction in uncertainty of the perceptual estimate that cannot be achieved by the more reliable single sense (Rohde, van Dam, & Ernst, 2016). In other words, the final percept is more accurate and precise than that of either of the two senses alone. In situations when the relative precision differs between the senses that are involved (e.g. vision is more precise than touch in estimating object size), the final percept is biased towards this more reliable sensory estimate (i.e. visual). This often results in one sense dominating the final percept. In situations where both senses are similarly reliable the optimal final percept would be the linear average of the two sensory estimates (see Figure 2A). However, it is important to note here that this is based on the assumptions made about the sources of uncertainty. That is, typically it can be assumed that sensory noise follows a Gaussian distribution, in which case optimal integration predictions can be estimated by a weighted linear average. Under specific conditions, i.e. when sensory feature space cannot be linearly mapped to the parameter space, Gaussian noise cannot be assumed (Knill, 2007; Saunders & Knill, 2001). However, in most cases sensory noise either follows a Gaussian distribution or can at least be well approximated by it (Hartcher-O'Brien, Di Luca, & Ernst, 2014; Rohde et al., 2016).

Mathematically, statistically optimal integration can be approximated by Maximum Likelihood Estimation (MLE). This bears the advantage that predictions about optimal integration performance can be modelled and compared to behavioural performance that is experimentally measured, allowing us to quantify the perceptual benefit of multisensory integration (Ernst & Banks, 2002; Helbig et al., 2012; Rohde et al., 2016). In order to do so, individual measures of sensory precision need to be established first for every sense separately. This is crucial as it takes into account the inter-individual variation in sensory precision within and across senses (Murray, Thelen, Ionta, & Wallace, 2019; Stevenson, Zemtsov, & Wallace, 2012). Measures of precision for each sensory cue *i* inversely relate to the uncertainty σ_i^2 of the unisensory estimate E_i . This unisensory uncertainty is described by the variance of its likelihood function (see Figure 2A). In other words, a smaller variance in cue estimation is indicative of higher perceptual precision, and vice versa. As optimal integration takes into account the relative precision of the two

estimates, this can be expressed as sensory weight w_i for each unisensory cue (here *j* and *k*) through:

$$w_j = \frac{\frac{1}{\sigma_j^2}}{\left(\frac{1}{\sigma_j^2} + \frac{1}{\sigma_k^2}\right)} \quad \text{and} \quad w_k = \frac{\frac{1}{\sigma_k^2}}{\left(\frac{1}{\sigma_j^2} + \frac{1}{\sigma_k^2}\right)}$$

As perceptual weights describe the relative precision of two (or more) estimates, w_j and w_k add up to 1. Following from this, the bimodal, optimal estimate E_{bi} is given by:

$$E_{bi} = w_j \cdot E_j + w_k \cdot E_k$$

This shows that lower sensory uncertainty leads to a higher perceptual weight and consequently to a stronger influence on the combined perceptual estimate. An example of such uncertainty-related weighting is displayed in Figure 2A (based on Ernst & Banks, 2002; Rock & Victor, 1964). In this example, participants had to judge the size of an object using either vision, touch, or both. A distortion lens that was installed between the participant and the object created a cross-modal conflict between visual and haptic estimates (i.e. the object looked bigger than it felt). As vision is typically the more reliable sense for estimating object size (in adults), the visual estimate shows less uncertainty ($\sigma_V^2 < \sigma_H^2$) and therefore a higher weight ($w_V > w_H$). Consequently, the final estimate E_{bi} , which describes the point of maximum likelihood, gets biased towards the more strongly weighted, visual estimate E_v .

However, another important feature of optimal multisensory integration can be noted in this example, which is the reduction in sensory uncertainty. In fact, for multisensory integration to benefit perceptual precision, the final estimate needs to be less uncertain (i.e. more precise) than the best unisensory estimate alone. Mathematically, this reduction in bimodal precision resulting from optimal integration can be calculated as:

$$\sigma_{bi}^2 = \frac{\sigma_j^2 \, \sigma_k^2}{(\sigma_j^2 + \sigma_k^2)}$$

Where σ_{bi}^2 describes the variance (uncertainty) of the bimodal perceptual estimate, while σ_j^2 and σ_k^2 represent the variance of each single sensory estimate. Here, the reduction in uncertainty is greatest when uncertainty within the two unisensory estimates is approximately equal. Note that optimal integration would always predict the uncertainty of the bimodal estimate (σ_{bi}^2) to be lower than the uncertainty of either of the two

unimodal estimates (σ_1^2 or σ_2^2). This reduction in uncertainty signifies the perceptual benefit of multisensory integration. In the example displayed in Figure 2, this is shown by a narrowing of the bimodal likelihood function compared to either of the unimodal functions.

A paradigm that is commonly employed to assess whether cue combination results in optimal integration as predicted by the MLE model is the two-alternative forced-choice (2AFC) paradigm (Ernst & Banks, 2002; Helbig et al., 2012; Knill & Saunders, 2003; Nardini, Jones, Bedford, & Braddick, 2008; Petrini, Remark, Smith, & Nardini, 2014). Here, participants are presented with two stimuli that differ in one parameter of interest (e.g. size, shape, location, timing), which can be assessed with at least two senses. They are then asked to discriminate between the two stimuli based on the feature of interest. For example, if object size is the feature of interest, participants would be asked to tell which of two objects is bigger than the other. Thereby, one stimulus is kept constant (standard stimulus) while the other stimulus is varied parametrically (comparison stimulus). The standard stimulus then serves as a reference against which responses to different comparisons can be mapped. Mapping out responses across the stimulus feature space (e.g. all available comparison sizes) allows to derive discrimination thresholds. The discrimination threshold serves as a measure of perceptual sensitivity, as it describes the minimum difference between two stimuli that is necessary for the participant to reliably tell a difference in the right direction (e.g. a physically bigger object is reliably perceived as bigger). This measure can be used to assess the predicted reduction in uncertainty described above. That is, by assessing the individual discrimination thresholds using unisensory stimuli, e.g. visual object size and haptic object size separately, the variances for each sensory cue σ_V^2 and σ_H^2 can be estimated. From the unisensory variances, model predictions about the integrated cue variance σ_{bi}^2 can be derived. This prediction can be compared against the experimentally determined variance by means of a bimodal discrimination threshold. Optimal cue integration is typically statistically assessed on the group level. Here, the group-averaged, measured bimodal discrimination threshold σ_{bi} is compared against both the unisensory discrimination thresholds σ_V, σ_H as well as the predicted bimodal threshold σ_{p*bi} . In order to assume optimality of cue integration, the measured and predicted bimodal estimates would not differ from each other, while the measured bimodal estimate would differ from both unimodal estimates (Gori, Del Viva, Sandini, & Burr, 2008; Rohde et al., 2016).



Figure 2: Statistically optimal integration of visual and haptic cues in an object size estimation task. (A) Probability functions indicating the likelihood of the object being perceived as a certain size. Bimodal likelihood function (grey) is the weighted product of the two unimodal Likelihood functions, depending on the uncertainties in the visual (σ_V) as well as the haptic (σ_H) functions. E_{bi} indicates the combined perceptual estimate of visual (E_V) and haptic (E_H) unimodal size estimates. An increase in visual noise leads to a stronger weighting of the haptic Likelihood function, thereby 'pulling' the bimodal size estimate closer to the haptic one. (B) Illustration of visuo-haptic size estimation task, whereby participants judge the size of an object using vision and touch. Introducing a conflict between visual and haptic size helps determining the weights placed on the combined unisensory estimates. (C) Psychometric functions indicating the relationship between actual stimulus size and the proportion of comparison stimuli being perceived as larger than a standard stimulus. Visual and haptic cues of the standard stimulus give discrepant information (Δ). The discrimination performance indicated by the functions can be experimentally measured and informs us about the bias and precision of the bimodal estimate (as indicated in panel A). Figure reprinted with permission from Rohde et al., 2016.

The Maximum-Likelihood Model has been frequently applied in studies assessing the perceptual benefits of multisensory integration in human and non-human animals (Battaglia et al., 2003; Billino & Drewing, 2018; Ernst & Banks, 2002; Fetsch, Turner, DeAngelis, & Angelaki, 2009; Gori, Sandini, & Burr, 2012; Gu, Angelaki, & DeAngelis, 2008; Helbig & Ernst, 2007) and is considered one of the most successful approaches to describing and predicting human perceptual performance (Chandrasekaran, 2017; Landy, Banks, & Knill, 2012; Trommershauser, Körding, & Landy, 2012; Van Dam, Parise, & Ernst, 2014). Furthermore, the optimal observer model has also been shown to explain well the underlying neural mechanisms of multisensory integration (Boyle, Kayser, & Kayser, 2017; Fetsch, Deangelis, & Angelaki, 2013; Fetsch, Pouget, Deangelis, & Angelaki, 2012; Helbig et al., 2012; Rohe & Noppeney, 2015).

A great amount of our knowledge on the neural processes underlying multisensory attributed emergence technologies integration can be to the of like electroencephalography, functional brain imaging or transcranial magnetic stimulation (e.g. Beauchamp, Pasalar, & Ro, 2010; Dekker et al., 2015; Foxe et al., 2002; Giard & Peronnet, 1999; Helbig et al., 2012; Merabet et al., 2008). However, the first evidence for neural multisensory processes comes from Stein and Meredith's studies on single neurons (Meredith & Stein, 1983; Stein & Meredith, 1993). They recorded electrical signals of neurons in the superior colliculus (SC) of cats in response to auditory, visual and audiovisual stimuli. Neurons in this region, but also other regions, responded to all stimuli types, but showed different response strengths towards unimodal (auditory, visual) and multimodal (audio-visual) stimuli, with multimodal stimuli evoking greater responses than unimodal ones (see Figure 3). Most strikingly, these enhanced responses were even greater than the sum of the responses towards unimodal stimuli ("super-additivity"). Besides an increase in response strength, multisensory integration has also been characterized by shortened response latencies, meaning that single neurons respond faster to multisensory than unisensory stimuli (Rowland & Stein, 2007).



Figure 3: Example of super-additive responses during integration of auditory and somatosensory information in a neuron of the cat anterior ectosylvian sulcus (AES). The top panel indicates the spatial overlap between the cat's auditory and somatosensory receptive fields used for stimulus presentation (shaded regions). Presentation of auditory (A) or somatosensory (S) stimuli alone elicited only few neural responses, as can be seen in the raster plots and histograms. Simultaneous and spatially coinciding presentation of auditory and somatosensory stimuli evoked a significantly stronger response. The bar graph at the bottom shows a summary of neural responses to both unimodal (A, S) and simultaneous bimodal (AS) stimulation. This neuron exhibits a larger response enhancement to the bimodal stimuli presentation compared to the sum of the two unimodal ones (**p<0.01). Figure reprinted with permission from Wallace, 2004.
There is also increasing evidence that multisensory processing even takes place in what are normally considered primary sensory areas, leading some to theorise that the brain is organized in a "metamodal" (Kim & Zatorre, 2010; Pascual-Leone & Hamilton, 2001; Proulx, Brown, Pasqualotto, & Meijer, 2014), or "supramodal" (Matteau, Kupers, Ricciardi, Pietrini, & Ptito, 2010; Ricciardi et al. 2014; Struiksma, Noordzij, Neggers, Bosker, & Postma, 2011), fashion. That is, rather than having a sensory-based organization, the brain instead has a computationally-defined functional architecture that is task-based (Pascual-Leone & Hamilton, 2001). It therefore might be best to try and consider the brain from a multisensory rather than unisensory perspective (Ghazanfar & Schroeder, 2006).

Development of multisensory integration

During infancy and childhood the human sensory systems develop at different rates (Burr & Gori, 2012). Touch usually develops first, followed by the vestibular, chemical and auditory systems, and then finally the visual system (Gottlieb, 1971). However, not only do our distinct sensory systems develop at different rates but also the different components of each of these systems. For example, the perception of some basic visual and haptic properties like colour, contrast, some forms of motion as well as object shape and weight develops within the first year of life (Atkinson, Braddick, & Moar, 1977; Atkinson, 2000; Streri, Lhote, & Dutilleul, 2000; Striano & Bushnell, 2005). Other skills like auditory frequency and temporal discrimination develop throughout infancy (Olsho, 1984; Trehub, Schneider, & Henderson, 1995) whereas capacities like the extraction of speech signals in overlaid noise but also the active haptic perception of objects develop rather late and often do not reach adult-levels before late childhood (Elliott, 1979; Gori et al., 2012; Johnson, 2000). This shows that there is not one straightforward rule that dictates the development of perceptual processing but that it is a complex and multifaceted process. In fact, given ongoing perceptual learning and neuroplasticity, certain aspects of sensory processing certainly continue to change over time, even into adulthood (Proulx et al., 2014).

The ability to use redundant sensory cues to enhance perception seems to be present very early in life. For example, infants and later young children find synchronous redundant stimuli across visual and auditory modalities very salient (e.g. Bahrick & Lickliter, 2000, 2004; Bremner et al., 2011; Lewkowicz, 1996, 2000; Morrongiello, Fenwick, & Chance,

1998). That is, human infants during the first year of life (Lewkowicz, 2010) have been shown to process audio-visual information on the basis of temporal synchrony rather than of sensory reliability. The reliance on temporal and spatial correspondence between cues is a stronger binding factor until late childhood. Indeed, the ability to filter out irrelevant information across modalities when cues are in temporal synchrony starts rather late (not before 11 years of age; Petrini, Jones, Smith, & Nardini, 2015). Similarly, speech pattern recognition and speech perception become more accurate around that age range (Eisenberg, Shannon, Martinez, Wygonski, & Boothroyd, 2000; Petrini & Tagliapietra, 2008). Barutchu et al. (2010) hypothesised that attention and other higher order cognitive processes regulate cross-modal integration and that the maturation of these processes delays the development of multisensory integration (Barutchu et al., 2010). However, it has not been until recently, that fMRI studies have shown that cue integration properties in the visual cortex only develop around the same age (Dekker et al., 2015, see Figure 4 and 5). Until then, children typically exhibit sensory dominance, whereby one sense dominates the final percept, instead of being integrated with information from the other sense (Gori et al., 2008; Petrini et al., 2014, see Figure 6). Here, sensory dominance depends on the task as well as the sensory modalities that are being used. For example, while vision is the more robust sense for assessing the orientation of objects, touch is more reliable for assessing object size. Therefore, in a visuo-haptic size discrimination task, children tend to rely mostly on the haptic information, while during object orientation discrimination, vision dominates the final percept (Gori et al., 2008).



Figure 4: Detection mechanisms & integration criteria of visual cue integration during depth perception. (A) Participants were presented with dot displays that used binocular disparity (differences in dot positions between the two eyes) and relative motion (movement speed of target dots relative to surrounding dots) to simulate depth of a target square that was either in front or behind its surround. Depth estimators for both stimuli are displayed as bivariate Gaussian distributions (as indicated by the blobs in the motion-disparity space). In the area where the conflict is largest, fusion of both stimuli (left) would result in a combination of the cues and reduce variance, that is, the two cues would be integrated. A mechanism that would treat the sensory information streams independently (right) would result in a greater separation of the stimuli. Using these two cues, participants were tested on two single cue and two combined cue conditions: D: disparity was altered while relative motion was kept constant; M: relative motion was altered while disparity was kept flat; DM: both cues conveying congruent information (e.g. both cues suggested the target square was near); D-M: both cues conveying incongruent information (e.g. disparity suggested that the target was far while motion suggested it was near). (B) Following

the two different mechanisms explained before (fusion or independence), two predictions can be made for each scenario: Criterion 1: the sensory fusion mechanism (left panel) would predict that sensitivity is enhanced when both sensory cues provide congruent information, compared to incongruent information. Following the independence mechanism, bimodal sensitivity would not be affected by congruency. Criterion 2: fusion of sensory information would predict sensitivity to be greater than the quadratic sum of single cue sensitivity when both cues provide congruent information. On the contrary, the independence mechanism predicts that sensitivity of DM is equal to the ideal observer prediction (quadratic sum).



Figure 5: Pattern classification fMRI results at different ages. (A) Images depict the scanned brain areas and the regions of interest (ROIs) for two subjects. (B) ROI analysis shows d-prime (accuracy) with near versus far stimulus depth decoded from activation patterns in area V3B. For comparison, the same is shown for area V1. Small bar plots in top left corner represent perceptual performance (1/sigma) of the same subjects – larger values indicate better depth sensitivity. Comparison of 8-10.5 year olds and 10.5-12 year olds shows a change in processing mechanisms, indicating that older children integrate information (fusion). Activation patterns in V3B show that accuracy for congruent cue information exceeds accuracy from conflicting cues as well as single cue predictions. D: altered disparity and constant relative motion; M: altered relative motion and flat disparity; DM: disparity and relative motion convey congruent information; D-M: disparity and relative motion convey incongruent information. Figures taken and adapted with permission from Dekker et al., 2015.



Figure 6: Late development of audio-haptic integration measured in a size discrimination task. Mean size discrimination thresholds give the minimum size difference between two stimuli that is required for the observer to tell that there is a difference between them. This means that smaller discrimination thresholds indicate higher precision. The red points indicate the discrimination threshold for observers using touch only (σ_H) while the blue triangles stand for the same individuals using hearing only (σ_A). The green squares show discrimination thresholds for the average MLE model prediction (black squares), which was calculated individually for each subject to predict performance from statistically optimal multisensory integration. The predicted threshold for bimodal size discrimination was calculated using the equation: $\sigma_{HA}^2 = \sigma_H^2 \cdot \sigma_A^2 / (\sigma_H^2 + \sigma_A^2)$. Error bars represent the standard error of the mean. Figure taken with permission from Petrini et al., 2014.

Petrini and colleagues (2014) used an audio-haptic size discrimination task to assess optimal cue integration in adults and in children aged 5-11 years. They asked their participants to judge which of two objects is bigger by wither tapping them with their hand, or by listening to the sound they make, or by using both senses at the same time. Using the MLE model, they found that an optimal reduction in uncertainty was only achieved in the adult group, but not in children up until 11 years of age (see Figure 6). While children exhibited haptic dominance, adults relied more on the auditory cue when discriminating object size. While the reasons behind the late development of multisensory integration are not quite clear, Gori et al.'s (2008) 'cross-calibration' hypothesis proposes a compelling solution. Their idea states that, before optimal integration emerges, the

senses "teach" (calibrate) each other during perceptual development. That is, the most robust sense calibrates the less robust sense to accurately process the perceptual properties of objects and people in the environment. As the relative sensory reliability depends on the stimulus properties that are being processed, the task at hand determines which sense calibrates the other. For example, when visual and auditory cues are present during object localization, the more robust visual information will dominate the final percept.

The higher importance of calibration during childhood might be due to a trade-off between optimal multisensory integration and physiological development. Hereby, it has been proposed that calibration takes the rapid physiological changes that occur in childhood into account (Gori et al, 2010). For example, children's limbs grow rapidly and the separation and length of eyes increase. These changes must be accounted for by the perceptual systems. Hence, it would be disadvantageous to integrate imprecise and inconsistent estimates, but beneficial to first refine them in each sensory system alone through cross-modal calibration.

Perception and sensory impairment

So far we have seen how sensory abilities develop and achieve optimality under typical conditions. We know that, usually, performance is best when redundant information is present, providing a rich, reliable signal. However, as we previously mentioned, there might be situations in which the input from either one sense or several senses is unavailable or is suddenly lost. Blind and deaf individuals lack inputs from important sensory modalities, which in turn greatly affects their quality of life. For example, a task such as finding the way home that may appear easy to sighted individuals could be quite demanding for blind or visually impaired individuals. Similarly, crossing a road, finding certain objects in unfamiliar places, and participating in conversations to enhance social bonds are other examples of demanding tasks in absence of vision or hearing. Indeed, when one or more sensory modalities are missing or impaired it becomes much clearer how multisensory perception is essential: in order to cope with the lack of information from the missing sense, the remaining senses have to take primary roles in representing and identifying stimuli in the environment.

Worldwide there are about 39 million people who are completely blind. Another 246 million people live with some form of visual impairment (World Health Organization, 2014). However, it is estimated that 80% of these cases could be prevented or cured. This is because the great majority of people with visual impairment live in developing countries, where treatment of some of the major causes for visual impairment, i.e. cataracts and glaucoma, is limited (World Health Organization, 2014). Furthermore, there are currently about 360 million people worldwide with disabling hearing loss, 32 million of whom are children (WHO, 2014). People with both forms of sensory impairment are at the highest risk of social and emotional discrimination (Bristol City Council, 2014). Sight loss creates huge barriers for many aspects of everyday life, from traveling, leisure or the use of technology to employment, Compared to the sighted working age population, employment rates amongst blind and visually impaired individuals are considerably lower (Slade & Edwards, 2015). Depending on the level of residual vision, only 10-25% of visually impaired and blind individuals in the UK are in paid employment (Slade, Edwards, & White, 2017), compared to 75% of the general population (Office for National Statistics, 2017). This not only places an economic burden on society (Pezzullo, Streatfeild, Simkiss, & Shickle, 2018) and exemplifies a prevailing lack in the provision of equal chances for individuals with visual impairment, but highlights the increasing difficulty with which everyday tasks can be mastered if vision is absent or impaired. In fact, poor mental health outcomes are more prevalent amongst visually impaired individuals than in typically sighted individuals (Petch & Mukhopadhyay, 2016) and increased psychological stress as a result of visual degradation has been shown to even accelerate the progression of vision loss (Sabel, Wang, Cárdenas-Morales, Faiq, & Heim, 2018). Limited access to valued activities as well as social isolation are major contributing factors to the association of visual impairment and low mental health (Petch & Mukhopadhyay, 2016), emphasizing how limited accessibility to sensory information can affect an individual's wellbeing and quality of life (Burmedi, Becker, Heyl, Wahl, & Himmelsbach, 2002; Pezzullo et al., 2018). This highlights the necessity to develop methods and technologies that allow the individual to perceptually adapt to their environment in order to master the demands of everyday life and to facilitate independence and equal opportunities. In order achieve the best rehabilitative outcome, however, we first need to gain a deeper understanding of how the perception is affected in sensory impaired individuals, and the neural mechanisms that support this process. While this chapter largely discusses perceptual adaptation and technological

rehabilitation for the hearing and visually impaired, the latter can also be understood as models for other sensory impairments. Up until now most research on the perceptual adaptation to sensory impairment has been focusing on visual and auditory deficits, making these the best understood sensory systems. As mentioned above, vision provides the most reliable information about the nature and position of objects (Tong, 2018) while audition is more reliable in estimating the temporal aspects of different sensory events (McDermott, 2018). Hence, visual and auditory information are crucial for many basic tasks such as orienting and identifying objects in the environment, shifting attention towards important events or for appropriately interacting with others. It is therefore not surprising that deficits in these senses have attracted the interest of researchers worldwide aiming to restore or compensate for these types of sensory loss. However, in order to develop successful methods and devices that help the visually or hearing impaired in daily life tasks, we first need to understand how the absence of vision or audition affect perception in general and, more specifically, the use of the other, remaining senses.

How vision loss affects perception in the remaining senses

For a long time, it has been widely accepted that the absence of visual input improves information processing in the remaining senses. This has been supported by research showing that visually impaired individuals display equally good or sometimes even superior performance on auditory localization (Lessard, Pare, Lepore, & Lassonde, 1998; Röder et al., 1999; Voss et al., 2004), tactile discrimination (Alary et al., 2008; Goldreich & Kanics, 2003, 2006), memory tasks (Amedi, Raz, Pianka, Malach, & Zohary, 2003; D'Angiulli & Waraich, 2002; Pasqualotto, Lam, & Proulx, 2013; Raz, Striem, Pundak, Orlov, & Zohary, 2007) and enhanced musical and verbal processing abilities (Amedi et al., 2003; Hugdahl et al., 2004; Pasqualotto, Lam, et al., 2013).

However, an increasing number of studies have yielded contrasting results. Many of them demonstrate that the loss or impairment of vision affects the way space is perceived in the remaining senses (for reviews see Pasqualotto & Proulx, 2012 and Ricciardi, Bonino, Pellegrini, & Pietrini, 2014). Auditory localization of objects, for example, has been extensively studied in human and non-human participants (Konishi, 2000, see Collignon, Voss, Lassonde, & Lepore, 2009 for a review). Clearly, this can be attributed to the central role object localization plays in many independent daily-life tasks and its strong

dependence on visual information. Some studies have shown that blind individuals show normal or even supra-normal auditory localization performance in the far space as well as near space, whereas haptic information might drive the calibration of auditory space through sensory-motor feedback in the latter (Fieger, Röder, Teder-Sälejärvi, Hillyard, & Neville, 2006; Lessard et al., 1998; Voss et al., 2004). Other studies found that in earlyblind individuals the representation of auditory space in the lower sagittal plane is compromised in comparison to sighted individuals (Finocchietti, Cappagli, & Gori, 2015). The authors argued that this is due to a disruption of audio-visual cross-sensory calibration (Gori, Sandini, Martinoli, & Burr, 2014). Thereby, auditory localization in the horizontal plane could yield enhanced performance because certain cues, which are used by the brain to decode sound source location, i.e. interaural loudness difference (ILD) and interaural time difference (ITD) would still provide a reliable location estimate (Moore, 2003). In general, the human auditory system can take advantage of both of these types of information, or each one separately if they are not both present. An advantage of sound localization in the horizontal plane has also been supported by earlier studies (Lessard et al., 1998; Voss et al., 2004). Sound location in the sagittal plane, on the other hand, can only be mapped based on the pinna-related spectral shape cues, which are less accurate than interaural time or loudness differences (Zwiers, Van Opstal, & Cruysberg, 2001). As vision is usually thought to have a stronger impact on auditory localization in the vertical dimension (Lewald, 2002), and additional visual information is not available in the blind, this may result in poor localization and ultimately disrupted auditory spatial maps.

While most studies that have reported auditory localization enhancement in early-blind individuals employed tasks asked participants to localize single sounds in the horizontal plane (e.g. Lessard et al., 1998; Röder et al., 1999), these tasks do not require a coherent metric representation of space. However, judging the relative location between two or more sounds requires a clear mapping of Euclidian space. More recent studies employed spatial bisection tasks, whereby the relative spatial position of consecutively presented sounds within the horzontal plane needs to be judged (Gori et al., 2014; Vercillo, Burr, & Gori, 2016). These studies showed that the spatial representation of congenitally-blind individuals is severely compromised. While this was found in both adults (Gori et al., 2014) and children (Vercillo et al., 2016), the latter further showed developmental delays in auditory localization of single sound cues (Cappagli & Gori, 2016). Notably, the age of blindness onset seems to play a critical role in the development of non-visual spatial

abilities. For example, while in Finocchietti et al.'s study (2015) early-blind individuals showed impaired audio localization in the lower sagittal plane, late-blind individuals did not. This group's responses were similar to those of sighted participants. This might indicate that cross-modal calibration builds up the foundations for understanding physical properties in the environment at an early age, when plasticity is high (Putzar, Goerendt, Lange, Rösler, & Röder, 2007).

Other studies have examined the cross-modal effects of visual deprivation on somatosensory processing. While blind individuals are often referred to – and reported to – have superior tactile acuity (Goldreich & Kanics, 2003; Norman & Bartholomew, 2011) there is also evidence of an impairment of haptic recognition and orientation discrimination abilities (Gori, Sandini, Martinoli, & Burr, 2010; Pasqualotto & Newell, 2007). However, the effects of visual deprivation on multimodal processing have been less intensely investigated. In a recent study Guerreiro, Putzar, and Röder (2015) compared neural responses of sighted participants in an audio-visual task to those of participants, who were blind at birth but regained sight following surgery within the first two years of life. Using functional magnetic resonance imaging the authors found that early-blind, sight-restored individuals did not exhibit multisensory integration of audio-visual cues (Guerreiro et al., 2015). From this they concluded that early visual experience lays the physiological and functional foundations for audio-visual multisensory integration in later life.

The idea of developmental periods during which perceptual learning is enhanced, indeed, is not new and many studies have looked at (perceptual) learning in the light of heightened neural plasticity during early life. The concept of neural plasticity comprises the ability of the central nervous system to adaptively modify itself in its own structural and functional organization on the single cell level (Ahissar et al., 1992; Paul Bach-y-Rita, 1988). During learning, for example, neural plasticity allows the central nervous system to adapt to functional needs. In terms of perception, this structural and functional reorganization is driven by individual, perceptual experience that often is of multimodal nature. During an individual's development there appear to be time windows of high neural plasticity, called sensitive periods (Knudsen, 2004). Sensitive periods are more likely to occur when organisms are uncertain about environmental conditions or are not constrained in their phenotype-environment match (Fawcett & Frankenhuis, 2015). For example, as babies can be born into different types of environments and are not prenatally

adapted to a certain one, it not surprising that most sensitive phases happen very early during development. During these periods, perceptual experience can have a strong impact on brain development in the form of structural (Collignon et al., 2013; Ricciardi et al., 2014) and functional (Voss, 2013; Merabet & Pascual-Leone, 2010) changes. Early studies on animals have shown that experiences within these sensitive periods, during which the individual learns to recognize certain aspects of its environment (e.g. its parents, Hess, 1972; Lorenz, 1937), have long-lasting effects on the individual's behaviour (Immelmann, 1972). Learning that occurs during this time period therefore "lays the foundation for future learning" (Knudsen, 2004, p.1412). So what does this mean for sensory deficits – what does the brain do in order to gain a reliable percept of the environment when input from one sensory modality is not available during phases of heightened plasticity?

Compensation of sensory loss through cortical reorganization

People that lose one sense due to disease or damage of the sensory organs (e.g. retina in the visual system, cochlea in the auditory system) do not necessarily lose the capacity to perceive or process stimuli that are usually derived from these sensory modalities (Bachy-Rita & Kercel, 2003). In case of sensory input absence, the central nervous system responds with neural plasticity to functional needs. The increased use of the remaining senses requires structural re-organization in the intact cortical areas of these senses. For example, blind experienced braille readers have enlarged cortical regions in the somatosensory cortices representing their "reading" finger (Pascual et al., 1993). Further, cortical auditory areas expand and become more refined in congenitally blind, compared to sighted individuals (Elbert et al., 2002; Huber et al., 2019), which is also reflected on the behavioural level in an enhanced ability to discriminate frequencies and process language in the blind. These, among numerous other examples, show that structural and functional reorganization of the brain imply numerous benefits for the individual as it allows for a better use of sensory information derived from the remaining senses. At the same time, however, neural reorganization can also bear potential negative consequences, especially in cases where senses are restored after a long period of deprivation (Fine, 2008). We will discuss the effects of sensory loss/deprivation duration on the functional outcomes of restoration later in this chapter.

The findings we mentioned previously do, however, not answer the questions of how cortical 'visual areas' in blind or visually impaired individuals get structurally and functionally reorganized. Will these areas deteriorate or will they re-organize so to take over the processing of different sensory information? There is growing experimental evidence that early visual deprivation does not lead to inactivation of the visual cortex, but that it is, in fact, followed by structural and functional cortical reorganization allowing auditory or somatosensory information to be processed in this area (Amedi et al., 2003; Cohen et al., 1997; Collignon et al., 2015; Collignon, Lassonde, Lepore, Bastien, & Veraart, 2007; Fine et al., 2003; Théoret, Merabet, & Pascual-Leone, 2004 but see Noppeney, 2007 for a review). This reorganization constitutes a compensation for visual loss through the enhanced processing of auditory and somatosensory information in presumptive "visual" areas. Indeed, several studies have shown that activation of the visual cortex in the blind is associated with sound and language processing, spatial imagery as well as braille reading and tactile discrimination (Cohen et al., 1997; Kupers et al., 2006; Struiksma et al., 2011; Uhl, Franzen, Lindinger, Lang, & Deecke, 1991; Vanlierde, De Volder, Wanet-Defalque, & Veraart, 2003). However, functional and structural cortical reorganization is not specific to blindness but extends to other sensory modalities and lack of such. For example, Levänen et al. (1998) made observations about the auditory cortex of a congenitally-deaf adult being actively involved in the processing of somatosensory information (Levänen, Jousmäki, & Hari, 1998). Interestingly, many studies reported noteworthy differences in information processing and reorganization between people who became blind at a very early age (or who were blind from birth), and those, who went blind later in life (see Noppeney, 2007). This may indicate that enhanced neural plasticity during childhood influences the brain's susceptibility for reorganization. It further highlights that the availability of sensory input critically determines the way in which our brains process sensory information and ultimately perceive the world.

Surely, plasticity forms the basis of learning to perceive any form of sensory input, at least at the neural level. However, as we have discussed earlier, perception and action are critically interwoven and their calibrating nature plays an important role in the development of ecologically relevant motor-skills and the ability to perceive and interact with objects in our environment (Proulx et al., 2015; Proulx, 2010). In order to achieve a reliable representation of objects, haptic perception depends largely on perceptual (intersensory) as well as action-perception (motor-sensory) processes. Whenever a motor

action is carried out, the central nervous system sends efferent motor commands to the actuator (e.g. hand muscles). At the same time, a copy of these motor commands is generated and matched with the afferent tactile and proprioceptive sensory feedback (Von Holst & Mittelstaedt, 1971). Integration and comparison of these two strands of information generates a specific haptic feedback and allows our brains to predict physical properties of the environment we interact with. However, this re-afference process really becomes important and improves haptic perception later in development (Gori et al., 2012). In typically developing children, who still undergo rapid physiological changes, internal motor command copies are more likely to be noisy. This might explain why haptic precision has been found to only reach adult-like levels in early adolescence (Gori et al., 2012). Crucially, while perception could not properly function without motor action (e.g. feeling the texture or shape of surfaces, scanning an objects properties with the eyes), action heavily depends on sensory feedback. These two systems should not be considered as independent components but rather as interwoven parts in a holistic actionperception-loop (Ernst & Bülthoff, 2004). In fact, the integration of sensorimotor information can play an important role in sensory rehabilitation therapy (see for example Cappagli, Finocchietti, Baud-Bovy, Cocchi, & Gori, 2017; Cappagli et al., 2019; Cuppone, Cappagli, & Gori, 2019).

Sensory rehabilitation in blindness

When thinking of sensory rehabilitation, one often thinks about the restoration of the impaired sense, which can be accomplished by, for example, surgical procedures or restoration therapy. However, rehabilitation can also be conducted through the remaining, intact senses via sensory substitution. The following sections give an overview of procedures and technologies that are currently available for people with visual impairments.

A number of useful assistive technologies like force-feedback devices (Zhu, Kuber, Tretter, & O'Modhrain, 2011) have been developed for blind users to navigate through the web. Generating haptic feedback via affordable gaming devices like the Novint Falcon or a mouse with motor feedback and adding auditory feedback enables blind and visually impaired people to explore usually vision-dominant computer programs like Excel or on-line websites (Doush, Pontelli, Simon, Son, & Ma, 2009; Oyamada, Bidarra, &

Boscarioli, 2013). Multisensory virtual environments that use touch and sound have further been used to convey geographic information to visually impaired users (Fisher, Unwin, Fisher, & Unwin, 2010; Lahav, Schloerb, Kumar, & Srinivasan, 2012; Lawrence, Martinelli, & Nehmer, 2009). However, these technologies and aids have a limited impact on everyday activities and the overall quality of life of blind and partially-sighted individuals.

Navigating from one location to another poses one of the major, daily challenges to people who cannot accurately perceive their environment through vision. From reading bus signs, street names or maps, to looking out for cars, obstacles, traffic lights or even other people – the world in which we navigate and the way in which important information is transferred is often not designed for visually impaired or blind people. They often have to rely on their remaining senses and therefore a lot of the information is simply not accessible to them. In 2014, Microsoft, Future Cities Catapult and Guide Dogs Association teamed up to tackle some of the mobility challenges people with sight loss face. As part of their collaborative project Cities Unlocked (Future Cities Catapult, 2016) they introduced a navigational headset that helps blind and visually impaired users to find their way through the city. The system relies on GPS information and a network of Bluetooth beacons installed and placed around the city. In this way the system combines the advantages of common navigation systems (e.g. turn-by-turn directions) with information about nearby points of interest or transportation updates. However, in addition to this navigation tool, users had still to rely on further mobility aids like guide dogs, white cane or some residual vision, because location information cannot effectively communicate important information that is necessary for a dynamic interaction with the immediate environment, such as the presence of obstacles, cars or other people. To increase independence and mobility it is therefore necessary to facilitate direct interaction with the environment, allowing the individual the gain attention-controlled access to information about the immediate environment in real-time. This can be achieved by either restoring the lost sense or by substituting information from the lost sense into information that can be accessed via the other, intact senses (sensory substitution). We will first describe sensory restoration techniques with a focus on the visually impaired and then introduce sensory substitution devices as a means of perceiving and interacting with the environment through the remaining intact senses.

Visual restoration

Our increasing understanding of sensory mechanisms and principles as well as the vast improvement of technology have opened new opportunities in the field of sensory rehabilitation (for a review see Maidenbaum, Abboud, & Amedi, 2014). One way to restore vision in the blind is through direct surgical procedures. Cataract surgery is the most commonly performed operation these days. This includes the replacement of the affected, clouded lens with an intraocular implant, a small plastic lens. Other approaches include using non-invasive technology that converts images into auditory or tactile displays (Proulx, Brown, et al., 2014; Proulx, Ptito, & Amedi, 2014). How might visual restoration be assessed? Visual acuity provides a measure of the distance at which two points are resolvable. Typically, optotypes in the form of letters or shapes are presented with decreasing size to determine acuity expressed as a Snellen fraction. The Snellen fraction is the ratio of the testing distance to the distance at which the smallest recognisable optotype subtends 5 arc-minutes, or 0.083 degrees.

Techniques like artificial retinal prostheses (Bloch, Luo, & da Cruz, 2019; da Cruz et al., 2013; Humayun et al., 2012; Zrenner, 2010) or the transplantation of photoreceptors (Yang et al., 2010) that aim to physically replace or bypass the damaged parts of the peripheral visual system offer treatment for people who lost vision through retinal damage (e.g., age-related macular degeneration). Over the last couple of years, new methods involving treatment with embryonic stem cells have been developed (Schwartz et al., 2014, 2015). This treatment is thought to restore vision through the repopulation of damaged retinal cells or the prevention from further degeneration of the cells. Stem cells are of special interest because of their ability to self-renew and high plasticity allowing for very individual and specialized application. Currently, however, the most common restoration approaches require retinal implants (for a review of some of the current models see Bloch, Luo, & da Cruz, 2019); for a more general review see Dagnelie, 2012).

One of these retinal prostheses, the Argus II (Second Sight; Ahuja et al., 2011; da Cruz et al., 2013; Humayun et al., 2012 for a review see Luo & da Cruz, 2015), is aimed at people with a malfunction of the photoreceptors (e.g. retinitis pigmentosa). This device comprises an external digital camera, integrated into the frame of eyeglasses, to capture images of the user's environment, an image processor, which converts the images into instructions that are sent to the retinal implant via a wireless antenna. These signals trigger the implanted array of 60 electrodes to emit small electrical pulses, thereby stimulating

the remaining retinal cells that transmit electrical impulses to the brain via the optic nerve. The brain then uses the transmitted visual information to create light pattern perceptions that can then be learned by patients through training. With this prosthesis, users have been shown to achieve a visual acuity of up to 20/1262 (Humayun et al., 2012) within a visual field width of 20 degrees. The second device currently available is the Alpha IMS sub-retinal implant (Retina Implant AG; Zrenner, 2002), which consists of an electronic wireless microchip that captures light falling onto the retina and stimulates the optic nerve, which then in turn delivers the signal to the brain. Studies reported that the highest acuity, that humans implanted with this chip reached, was 20/546 (Chuang, Margo, & Greenberg, 2014) within a visual field of 15 degrees.

However, visual acuity alone is not a sufficient measure of visual rehabilitation. In a recent study (Haigh, Brown, Meijer, & Proulx, 2013), using a sensory substitution device as an auditory display of images described more later, it was found that measuring visual acuity within sensory rehabilitation must consider additional variables taken for granted in normal acuity testing, such as consideration of the field of view provided by the technique. Hereby, one would still be classified as visually impaired if restricted by severe tunnel vision.

As for retinal implants, the resulting visual acuity and size of the visual field are determined by the amount and density of electrodes, this emphasizes that there are biological limits that set constrains to the success of this form of technology (Chuang et al., 2014). It is important to note that there are currently physical limitations on the best visual acuity possible through all kinds of rehabilitation methods, not only restorative.

In a three-year clinical trial, that followed 30 individuals, who received the Argus II visual prosthesis, Ho et al. (2015) found that the implant allowed subjects to perform basic visual functions like object localization or identifying motion direction and increased visual acuity (Ho et al., 2015). An earlier trial reported similar findings, showing that subjects were able to even identify letters and words (da Cruz et al., 2013). Notably, their findings also show that the age at transplantation is an important predictor for outcome success of visual restoration. However, this did not reveal whether patients really benefitted from the additional, visual information in more complex tasks they face in everyday life. As discussed above, one of the most demanding tasks for visual impaired individuals is navigating their environment and finding their way in it. To navigate, humans use visual

cues as well as self-motion information (Souman et al., 2009). A recent study by Garcia et al. (2015) investigated how well patients, who have been implanted with the Argus II visual prosthesis, could make use of the new, visual information to increase navigational precision. They tested four Argus II implanted patients and sighted individuals on a path reproduction and a triangle completion task, both in the absence and presence of an indirect visual landmark. Sighted participants wore goggles that only allowed a restricted field of vision and low visual resolution, similar to the visual field and resolution properties provided by the Argus II. The information from the visual landmark that was received by the sighted participants was sufficient to increase navigational precision. In Argus II patients, however, there were no such improvements in the path reproduction path (see Figure 7). Two patients showed a benefit similar to normally sighted subjects on the triangle completion task, however, compared to their sighted counterparts, the patients' navigational precision was higher when visual cues were absent. This indicates that, when individuals have been blind for many years and non-visual information becomes more reliable, the visual information provided by the Argus II retinal prosthesis might not be sufficient to increase performance on navigational, spatial tasks for which sighted individuals usually use vision. This also supports the notion that age of blindness onset and age of implantation (that is, how long an individual uses non-visual information for visual dominant tasks), coupled with the quality of visual information, have an impact on the effectiveness of visual restoration devices.



Figure 7: Performance of four patients implanted with a visual prosthesis (green symbols) and sighted individuals (blue stars) on a path reproduction (left) and a triangle completion (right) task. Sighted participants wore goggles that resembled the visual properties provided by the Argus II. All participants were tested in the absence and presence of a visual landmark. Depicted is the improvement of navigational precision with variable error (A) and accuracy with constant error (B) between trials where a visual landmark was absent or present. Shaded region represents the 95% confidence intervals computed from the performance of sighted individuals. Information from the visual landmark was sufficient to increase navigational precision approach a visual prosthesis. All patients showed a lower variable error when navigating without vision compared to normally sighted individuals. Two of four patients improved in precision on the triangle reproduction task in a similar way to sighted participants. Also, these two patients had lower constant errors without vision compared to controls. Figure taken with permission from Garcia et al., 2015.

Sensory substitution

Another way of targeting sensory rehabilitation in the blind is substituting the impaired input modality with an intact sense. That is, visual information can be conveyed via the other senses such as touch and hearing. Sensory substitution devices (SSDs) can provide information about various physical features and dimensions of objects by stimulating the intact senses (Paul Bach-y-Rita & Kercel, 2003; Meijer, 1992; Proulx, 2010). In comparison to sensory restoration using implants or prostheses, this rehabilitation approach offers a non-invasive and often cheaper alternative. SSDs aim to increase the users' independence and mobility by enabling them to "see" objects and people around them through their ears or skin, thereby allowing them to engage in direct and dynamic interaction with their environment (for a video demonstration see Proulx, 2014).

Some well-known, low-tech examples of sensory substitution are Braille reading or the long cane, which both convey information that is typically visually perceived in the sighted through tactile and proprioceptive cues (Paul Bach-y-Rita & Kercel, 2003; Sadato et al., 1996). This group of more traditional techniques and devices has been extended by modern SSDs, which benefit from the increasing use and development of technology. Most of these current SSDs can be subdivided into three main components: an input sensor that captures the information from the environment (e.g., visual scene), a processing unit that converts the input signal into another signal (e.g., sound representing the visual scene), and a human machine interface that transmits the converted information to the biological sensors of the user's substituting sensory system (Maidenbaum et al., 2014).

One of the first sensory substitution devices using modern technology and artificial sensory receptors was introduced by Paul Bach-y-Rita and colleagues in 1969 and transferred visual spatial information to the user via tactile stimulation of the skin. This 'Tactile Visual Substitution System' (TVSS) used an array of 400 tiny tactile stimulators, which were embedded into the back of a dental chair to transmit information captured by a video camera that was mounted on a tripod adjacent to the chair (Bach-y-Rita et al., 1996). The captured images were translated into two-dimensional patterns of vibration, which stimulated the skin on the back of the user. Bach-y-Rita was convinced that exploiting the advantages of the brain's plasticity would enable blind users to learn seeing with their skin. He and his colleagues, trained blind subjects with the TVSS to recognize simple patterns like lines and circles, and later even complex objects they encounter in

everyday life like telephones or chairs. They found that participants were able to "discover visual concepts such as perspective, shadows, shape distortion as a function of viewpoint, and apparent change in size as a function of distance" (Bach-y-Rita et al., 1969, pp. 963-64). Also, the device enabled a congenitally-blind person, who was trained with the system for only 25 hours to "see" the outlines of a candle's flame (Guarniero, 1974).

However, vision possesses specific properties that are challenging to translate into mechanic (such as in audition or touch) or chemical (olfaction) stimulation. How well visual concepts can be conveyed is strongly influenced by the processing capacity of the input-receiving modality (Kaczmarek, Webster, Bach-y-Rita, & Tompkins, 1991). A substantial body of work, much of it inspired by Treisman's Feature Integration Theory (Treisman & Gelade, 1980), has established the role of parallel processing in vision. That is, multiple features, and even multiple objects, can be processed simultaneously to a certain extent in vision. The non-visual modalities, in particular haptics, are instead often characterized by sequential or serial processing (Henriques & Soechting, 2005; Hsiao, Lane, & Fitzgerald, 2002). For example, when we explore an object with our hands we only get an idea of its shape by integrating the information we sample over time through moving our hands across the object's surface. During visual processing, on the other hand, we can determine the object's shape in an instance by simply looking at it (Loomis, Klatzky, & Lederman, 1991; Rieser, Hill, Talor, Bradfield, & Rosen, 1992). A recent review described how developmental vision has a special role in conveying information in parallel (Pasqualotto & Proulx, 2012). This is a key ability that is crucial for the integration of multisensory cues that are available within a close spatial and temporal time window and, hence, for perception and learning (Proulx, Brown, et al., 2014).

Sensory processing of spatial characteristics is furthermore determined by the density of sensory receptors. In touch, for example, skin sensitivity varies with the amount and density of mechanoreceptors and is lowest in the back and highest in the face and tongue. Researchers therefore modified the TVSS into a device, which is known as the BrainPort today. This device, instead of mechanically stimulating the skin on the back, uses electrotactile impulses to stimulate receptors on the surface of the tongue (Bach-y-Rita, Kaczmarek, Tyler, & Garcia-Lara, 1998), allowing for a higher resolution and increased portability.

Compared to the somatosensory system, the auditory system provides a higher spatial acuity and capacity for parallel processing, which makes the latter system a more efficient mean to translate and substitute visual information (Proulx, Brown, et al., 2014). Up to now, a number of visual-to-auditory SSDs have been developed. Peter Meijer invented the first of these systems, called "The vOICe" (Meijer, 1992). The vOICe algorithm converts visual images into sounds by scanning the image from left to right while transforming each pixel into a different sound. Thereby, brightness of the pixel is coded in loudness (i.e. amplitude) whereas its location in the vertical plane is represented by frequency (i.e. pitch), with increasing frequencies towards the upper part of the image and decreasing frequencies towards the bottom (see Figure 8). Due to this translation of visual information into sound, the spatial topography of the image is preserved, giving the user information of its environment that can usually only be assessed visually (an online demonstration can be found in Hadnett-Hunter, Brown, & Proulx, 2015). The preservation of visual spatial topography of the image makes visual-auditory SSDs a suitable tool for learning the mapping of space in an allocentric reference frame. Reference frames are a prominent feature in spatial navigation and are characterized by the organism learning to interpret the distances and positions of objects relative to one another to create spatial maps of its surrounding. Allocentric spatial maps can be used independently of the position of the own body and, therefore, allows spatial information to be accessed from different locations and orientations. Recent studies by Pasqualotto and colleagues showed that congenitally-blind individuals do not use an allocentric reference frame for spatial representation compared to sighted and late-blind subjects (Pasqualotto & Proulx, 2012; Pasqualotto, Spiller, Jansari, & Proulx, 2013), highlighting the role of developmental vision for the emergence of spatial cognition.

To find out if users could really learn to access information about an object's location ("where") and nature ("what") by practicing with this SSD, Proulx, Stoerig, Ludowig and Knoll (2008) blindfolded their participants for either 10 or 21 days continuously and asked them to train with The vOICe at home. Over the three-week period, participants that were using The vOICe in daily practice in their own homes improved markedly in speed and accuracy on a spatial localization task. A second experiment examined localization and grasping of natural objects placed on a large table using the same device (Auvray, Hanneton, & O'Regan, 2007). Also here the authors found improved performance on object localization and interaction. This suggested that they not only

understood "where" the objects were, but had access to features related to "what" the objects were, too: size, shape, and orientation.



Figure 8: An illustration of The vOICe sensory substitution device and its underlying conversion principles. Top left: a camera, hidden in "spy" glasses, is used as an input device to capture video images in the surrounding. The images are then transferred to a processing unit that runs The vOICe software to translate visual images into auditory 'soundscapes'. These soundscapes are played back to the user via a pair of headphones. Bottom left: Conversion principles of The vOICe. First, the image is converted into grey scale and then scanned from left to right. Objects that appear left in the image are played back early in the soundscape and louder to the left than the right ear. Objects on the right side of the image are played back later and louder to the right than the left ear (time & stereo panning). Objects that are positioned high in the image are translated into high pitch sounds, whereas objects that are low in the image are sonified with low pitch sounds. Brightness is converted into sound amplitude (loudness), that is, the brighter an object, the louder the sound. Right: example conversion of four different shapes and their corresponding soundscape images and waveforms. Reprinted with permission from Scheller, Petrini, & Proulx (2018).

The opportunity to manually change the viewpoint of the device establishes a link between vision-substituted (i.e. tactile or auditory) cues and sensorimotor cues, thereby facilitating perceptual-motor learning (Auvray & Myin, 2009). Herewith it also resembles natural vision, which requires active sampling of visual information in the environment through eye-movements in order to perceive complete objects or sceneries. Hence, the use of such technical rehabilitation devices does not equate to passively perceiving information from the environment, but actively engaging with it. Furthermore, Renier and De Volder (2010) showed that even early-blind individuals were able to learn and make use of visual depth cues, provided from visual-to-auditory sensory substitution. Astonishingly, only 135 minutes of training were sufficient to allow the blind individuals to learn this new information. Similar findings have been reported by Segond, Weiss, Kawalec and Sampaio (2013), who used visual-to-tactile sensory substitution.

Compared to the retinal prosthesis Argus II (60 pixels; Luo & da Cruz, 2015) and even to visual-tactile SSDs like the BrainPort (144 pixels; Kaczmarek, 2011), the technical resolution for The vOICe (25,344 pixels; Striem-Amit, Guendelman, & Amedi, 2012) is much higher. Arguably, technical resolution does not automatically translate into a better functional resolution, i.e. a better "visual" acuity (Striem-Amit et al., 2012). The latter makes up an important aspect for ascertaining both "what" and "where" information. Using The vOICe sensory substitution system, however, congenitally-blind individuals can achieve a higher visual acuity than with any other rehabilitation method (Striem-Amit et al., 2012), which is due to the capacity of the sensory system and the quality of its resolution.

Although the auditory and visual systems are not as comparable as the tactile and visual systems (as made obvious by the analogies between the skin and the retina, and by Bachy-Rita's decision to use tactile information for his original sensory substitution device), the ear has the potential to provide a greater amount of visual information to the brain than the skin. Moreover, even though the visual system might have the greatest information processing capacity and spatial acuity, the auditory system has the greatest temporal resolution. Therefore, a system that draws on the good temporal resolution capacity of the auditory system for the translation of visuospatial information might be best placed to provide high resolution sensory substitution. Indeed the superior visual acuity performance found with The vOICe might be due to not only the number of pixels that can be translated by the device but also to the higher information processing capacity of hearing versus touch.

Using visual-auditory SSD, Reich and Amedi (2015) showed that even higher-order processes like visual parsing, that are critically dependent on early visual experience, can be learnt by congenitally blind individuals (Reich & Amedi, 2015). The authors asked nine blind individuals (seven congenitally blind, one with weak light perception and one with some limited vision during her first year of life) to train their substituted 'vision' using The vOICe. The training lasted for approximately 70 hours and was split into two main stages. In the first stage participants learned to extract detailed 2D information from static images. In the second stage they used the device to actively engage with the environment and learn visual real world principles by interacting with their surroundings using, for example, hand-'eye' coordination. Following training, they were tested for visual parsing using 2D as well as 3D shapes. The stimuli and testing method was similar to that of Ostrovsky (2009) who tested three sight-restored individuals that underwent surgery between 2 weeks and 18 months prior to testing. Interestingly, the blind SSD users - who received information through a different modality - outperformed sightrestored individuals – who received this information via the natural way – on many visual tasks (Ostrovsky, Meyers, Ganesh, Mathur, & Sinha, 2009; Reich & Amedi, 2015).

A further advantage of The vOICe is that it is more affordable than alternative systems, thereby making it accessible to the vast majority of blind individuals with low economic status. This is important to keep in mind because, as mentioned above, the majority of the world's visually impaired population lives in low-income settings (World Health Organization, 2014).

What sensory substitution tells us about the blind (and sighted) brain

One of the greatest advantages of sensory substitution is that it allows individuals to access information from one sensory modality, which is not accessible through another modality. Here, SSDs can help us gain valuable insights into the neural processing of sensory information.

For a long time, the assumption that information from different sensory modalities is processed in sensory-specific brain areas, before getting integrated in higher associative areas, has been widely accepted (Felleman & Van Essen, 1991; Jones & Powell, 1970).

However, this traditional view has been challenged by studies reporting non-visual

information processing in presumptive visual areas in blind participants (Cohen et al., 1997; Ptito, Moesgaard, Gjedde, & Kupers, 2005; Struiksma et al., 2011; Uhl et al., 1991; Vanlierde et al., 2003). Indeed, a growing body of evidence about the generation of cross-modal responses in primary sensory areas (Calvert et al., 1999; Calvert, 1997; Foxe et al., 2002; Fu et al., 2003; Kayser, Petkov, & Logothetis, 2008; Kayser, Logothetis, & Logothetis, 2007) argues for a re-evaluation of the classical, modality-dependent model of brain organization. By using sensory substitution technologies several studies demonstrated that during substituted "seeing" the same neural networks that are recruited during normal vision are activated, both in sighted and in blind individuals (see Arno et al., 2001; Ptito, Moesgaard, Gjedde, & Kupers, 2005; Reich, Maidenbaum, & Amedi, 2012; Ricciardi et al., 2014 for reviews). These activations seem to occur independently of the user's level of training with the device (Arno et al., 2001) and are stronger in congenitally-blind individuals than in blindfolded sighted individuals (Ptito et al., 2005).

One example that shows how sensory processing is defined by the metamodal organization of the brain is the extraction of shape information from auditory soundscapes. Shape is a fundamental cue in determining the nature of an object and is usually assessed via visual or haptic exploration, whereas audition can only provide little information. Work with The vOICe showed that the processing of visual shape information from auditory soundscapes activated areas in the lateral occipital complex that are involved in visual and tactile shape processing (Amedi et al., 2007; Amedi, Jacobson, Hendler, Malach, & Zohary, 2002; Amedi, Malach, Hendler, Peled, & Zohary, 2001). The extraction of spatial information from auditory cues in this case it is not only limited to the auditory pathway but is extended to areas in the brain which typically process visual input. This shows evidence for an computation-based, i.e. metamodal, brain organization (James, Stevenson, Kim, Vanderklok, & James, 2011; Pascual-Leone & Hamilton, 2001; Proulx, Brown et al., 2014). That is, presumptive 'unisensory' cortical areas exhibit certain computations (e.g. spatial discrimination), irrespective of the inputted sensory modality.

Further support for the idea that the brain has a metamodal organization comes from studies investigating the generalization level of perceptual learning using visual-auditory and tactile-auditory SSDs (Kim & Zatorre, 2008; 2010). Here, the authors demonstrated that abstract shapes, which were learned through visual-to-auditory substitution, were

generalized to other modalities. They trained blindfolded, sighted participants to recognize these shapes by listening to their respective soundscape (Meijer, 1992, but see Figure 8). Following training, participants were not only able to match the pairs of visual/tactile shapes with the correct soundscapes but even showed generalization to novel auditory-visual and auditory-tactile pairings. What's more, in one of the studies (Kim & Zatorre, 2010) the authors found that participants, who have only been trained to match auditory-tactile shape pairings, were able to transfer this substitution learning to untrained visual stimuli. Taken together, these findings support the hypothesis that our brain is organized by the computation/function (James et al., 2011; Pascual-Leone & Hamilton, 2001; Proulx, Brown et al., 2014). Certainly, some low-level areas show a preference for the processing of information from one specific sensory modality, but it is becoming increasingly evident that these areas are not purely constrained to processing information from specific modalities, but are rather sensitive to specific stimulus features. This insight into the computational organization of the brain suggests that crucial information about the environment that is usually perceived visually, can also be conferred through other senses, thereby offering opportunities for rehabilitation of visually impaired individuals.

The impact of the age of blindness onset on sensory rehabilitation

In 1965, Wiesel and Hubel tested the effects of timing of visual deprivation on sight restoration in kittens. They lid-sutured either one eye or both eyes for the first three months and then reopened them. After three to 18 months, they looked at changes in anatomy and physiology of the visual system and found that visual deprivation in the first three months of life led to long-lasting changes in the visual pathway, even after a late prolonged period of visual experience (Wiesel & Hubel, 1965). Even after 5 years of visual experience following deprivation, recovery was very limited, however, this depended largely on the time of onset of visual deprivation (Hubel & Wiesel, 1970). This led them to conclude that when a lack of sensory input persists beyond a certain time period in life, neural reorganization will impede the functional restoration of vision with a similar to normal pattern of ocular representation.

These early studies of Hubel and Wiesel inspired other researchers to look into the effects of impairment onset on the outcome of sensory rehabilitation. A great number of studies

describe differences in information processing between early- and late-blind individuals (e.g. Burton et al., 2002; Cohen et al., 1999; Collignon et al., 2013; Fine, 2008; Sadato, Okada, Honda, & Yonekura, 2002; Stein & Rowland, 2011; Voss, Gougoux, Zatorre, Lassonde, & Lepore, 2008; for a review see Ricciardi et al., 2014). Many of these reported on the recruitment of neural matter in visual cortex regions for auditory (Bedny, Konkle, Pelphrey, Saxe, & Pascual-Leone, 2010; Collignon et al., 2013, 2015; Voss et al., 2008) and tactile (Burton et al., 2002;. Cohen et al., 1999; Sadato et al., 2002) processing (see Figure 9).



Figure 9: Schematic representation of the differences between congenitally-blind (CB) and lateonset blind (LB) individuals in how auditory information flows from A1 towards V1 via the Intra-Parietal Sulcus (IPS). This pathway is based on Collignon et al.'s findings using dynamic causal modelling analyses. Image taken with permission from Collignon et al., 2013.

However, how visual deprivation and cross-modal reorganization affect the functional, behavioural outcome in late-blind (compared to early-blind) individuals is not clearly established (for a review see Voss, 2013). That is, even if both groups show differences

in neural activation patterns, the behavioural outcome might be similar. Indeed, some studies find that behavioural performance is similar for early- and late-blind individuals and that they are even comparable to sighted individuals on spatial auditory tasks (Cappagli & Gori, 2016; Voss et al., 2004). In spatially-irrelevant auditory tasks (e.g. pitch discrimination) on the other hand, early- and congenitally-blind individuals performed better compared to the late blind (Gougoux et al., 2004), even when controlled for musical experience (Wan, Wood, Reutens, & Wilson, 2010). At the same time, it remains questionable if, even when sensory restoration in the late blind is successful, the individual really gains functional or behavioural benefits (Garcia et al., 2015). A recent study demonstrated a delay in the development of spatial auditory precision (Cappagli & Gori, 2016). The authors showed that blind and visually impaired adults, but not children, performed just as well as sighted individuals on an auditory localization task. This might point to the importance of much slower developing perceptual processes like multisensory integration (Gori et al., 2008; Petrini et al., 2014), especially in the unimpaired senses. That is, if children develop the ability to integrate information from the remaining, intact senses at a later age the resulting increase in information reliability allows for compensation of a disrupted auditory representation of space. It has been shown that the integration of audio-visual information is disrupted in individuals that were visually deprived for the first two years of life due to cataracts but regained sight following surgery (Guerreiro et al., 2015). Furthermore, there is evidence that auditorytactile interactions are affected by visual deprivation via different spatial attention mechanisms (Hötting, Rösler, & Röder, 2004). This emphasizes the importance for future research to look into the effects of multisensory integration during development for the construction of a precise representation of the environment and, ultimately, optimal behaviour. Understanding these processes will enable us to determine which rehabilitative methods will work best at different points in time. Furthermore, this reinforces the clear need to investigate if there are critical ages during which sensory substitution training will be most successful to rehabilitate sensory deficits.

Current advancements and future outlook in rehabilitation technology

As we have discussed so far sensory substitution devices as well as restorative technologies provide an elegant solution to increase our understanding of brain plasticity, brain organization as well as the development of perception and action. These

technologies enable us to learn about the ways in which the human brain processes information from different sensory inputs, how it copes with sensory deprivation and how cross-modal reorganization affects the outcomes of different types of sensory rehabilitation.

Visual restoration techniques like retinal and cochlear prostheses or embryonic stem cell treatment might hold great promises, however, at the moment their applicability is largely constrained by the complexity and risks of invasive treatment, long and arduous rehabilitation processes, as well as their cost and the rather low visual resolution they are able to achieve. These treatments are thus accessible to only a subgroup of visually impaired people who live in higher income settings and do only achieve limited visual rehabilitation.

Considering the trade-offs between effort (potential risks during surgery, financial costs, healing and training duration) and outcome ("visual" acuity, functional "vision", increase in interactive potential as well as independence and confidence), it is evident that sensory substitution devices offer a cheaper and less invasive alternative for rehabilitation compared to current sensory restoration methods. However, the distribution and acceptance of these devices encounters other hurdles. Besides their promising potential, the application of SSDs so far has not widely spread beyond controlled research settings (Maidenbaum et al., 2014). The progress in making these devices cheaper and less restricted to certain hardware by, for example, allowing them to work on common devices like smartphones, as well as developing successful training programs might facilitate the adoption of SSDs to everyday settings. Interactive training (Reynolds, Glenney, & College, 2012), for example, that not only takes perception but also action into account, should be incorporated into the process of SSD application for everyday tasks in the real world.

The current functional limitations of these devices arise from multiple domains: technological, such as the limited resolution of the device; modality, such as the resolution or nature of the sensory system substituting for vision; mapping algorithm (i.e. how sensory information from one sense is translated into information in the other sense), based upon similarities in feature processing across senses; and learning and plasticity, such as the required optimal training to achieve a long lasting multisensory perceptual learning (Proulx, Brown, et al., 2014) and a good level of generalization (Brown &

Proulx, 2013). There are certainly reasons to be optimistic for the future of sensory substitution. First, naïve users are able to perform not only above chance on spatial tasks with minimal training, but even to near ceiling degrees of visual acuity; moreover, even little training improves performance (Haigh et al., 2013) and such improvement can be maintained over several months and generalized beyond the specific information practiced during training (Brown & Proulx, 2013). These points are crucial and should be considered in the context of the development of normal vision. The current state of the art also suggest that different devices and modalities might be more appropriate when used for specific tasks. With the help of computer science-based knowledge about the limits and possibilities of interactive technology, this would enhance the potential of successful rehabilitation techniques for people with sensory deficits.

Conclusions and future outlook for sensory rehabilitation

Due to the complexity of our environment and our physical limitations, perception does not reflect reality but aims to create a representation of our world that is as veridical as possible. To help this process our central nervous system combines redundant information from several senses. Internal as well as external random noise has to be accounted for and determines the reliability of the different sensory modalities. Thereby, certain senses are better adapted to provide information for certain stimulus features than others. Due to its high spatial resolution and system specific features, vision plays a dominant role in spatial tasks, whereas audition grants the highest temporal resolution, giving rise to the metamodal (Proulx, Brown, et al., 2014) or supramodal (Ricciardi et al., 2014) organisation of the brain. An increasing body of literature suggests that during development the senses calibrate each other, with the most robust sense for one task teaching the less robust one (Cappagli, Cocchi, & Gori, 2017; Gori et al., 2008; 2010). Furthermore, evidence for heightened cross-modal plasticity, whereby the remaining, intact senses compensate for the lack of sensory input from the impaired modality, suggests that early sensory experience and resulting compensational changes scaffolds perceptual functioning later in life. Children that are deprived of sensory input early in life often show modality-specific impairment in the perception of their environment (e.g. poor spatial representation in the blind). However, processes like multisensory integration, which does not fully mature before late childhood (around the age of 10-12 years), might offer significant benefits for perceptual learning and rehabilitation of impaired spatial processing early in life.

In this chapter we have focused on uni- and multisensory perceptual processes with focus on the visually impaired and what interactive technology can be used to promote independence through rehabilitation. We have highlighted that, over the last few decades, great progress has been made in the development and application of technologies that facilitate autonomy and independence in people with visual impairments. While visual rehabilitation does not seem to offer an ideal solution to replace or restore vision to a satisfactory extent, insights into the way the brain processes sensory information in a computational fashion offer different ways of conveying visual information. Importantly, as the majority of people with visual impairments reside in developing countries and might have less chances of getting an expensive surgery, it is crucial to make alternative technology affordable to ensure it is accessible to everyone who needs it. However, increasing research in the field of sensory substitution and sensory restoration clearly is encouraging, and we look forward to advances in the design and application of affordable, interactive technologies with the aim to provide independence and confidence to those who have visual deficits and must deal with a world built by the sighted, for the sighted, without enough thought of inclusivity or accessibility. Research on sensory substitution and restoration further enhances our understanding of associated perceptual and multisensory processes and the brain as a plastic task-machine. While, for many years, our understanding of the sensory brain has been characterized by distinct, modular information processing domains, we are now accepting that a better representation of the brain requires what is now known as a metamodal or supramodal organisation.

To this end, we need to achieve a better understanding of the biological and psychological mechanisms underlying the development of multisensory integration in typically sighted and visually impaired individuals, as well as the neural basis supporting this process. This will allow us to determine under which conditions sensory impaired individuals really gain from using certain rehabilitative technologies. This will make answering the following questions a vital part of future research:

- How does sensory impairment or loss influence the development of multisensory integration and, more specifically, multisensory integration of the unaffected senses?
- Which visual rehabilitation techniques predict the best functional outcome for populations of a certain age and degree of neural reorganization?
- How can interactive sensory rehabilitation technologies like prostheses or sensory substitution devices be optimized and taken from a research-based setting to the wider, more general public?
- Is neural reorganization and plasticity due to sensory impairment and loss confined to primary sensory areas or extends to higher multisensory areas (e.g., posterior superior temporal sulcus/gyrus, inferior frontal gyrus)?

Chapter 1 – Conclusion

In this chapter, I outlined our current understanding of how our brain generates perception based on the sensory input it receives, and how interactive technologies can interface with the brain to aid perception in individuals with visual impairments. To this end, we have made great progress in understanding how single sensory perceptual processes develop, and how single sensory perception is cross-modally influenced by early sensory experience. However, as stated in the final open questions, one of the key challenges for future research remains to gain a deeper understanding of the mechanisms shaping the development of multisensory perception. That is, how does sensory impairment influence the development of multisensory integration of the unaffected senses, and is neural reorganization due to sensory impairment confined to primary sensory areas or does it extend to higher multisensory areas? The next three studies pick up on this question by assessing how multisensory perception changes throughout development, and how sensory experience influences its development.

In this thesis, I will focus on the role vision plays for the development of auditory-haptic size perception. Object size perception was chosen as size can be readily assessed through all three different senses – vision, touch, and hearing. Furthermore, this task allowed us to compare and build up on previous findings that used the same task with different sensory combinations and developmental age groups (Ernst & Banks, 2002; Gori et al., 2008; Petrini et al., 2014). Methodologically, the next chapters will adopt psychophysical and electrophysiological methods to assess both the mechanisms (Chapter 2, Chapter 4) and functional outcomes (Chapter 3) of multisensory integration for object size perception.

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Chapter 2: Active touch facilitates object size perception in children but not adults: a multisensory event related potential study

Chapter 2 Introduction

This study investigates the neural correlates of sensory dominance during object size perception in children. Gori et al. (2008) and Petrini et al., (2014) showed, behaviourally, that children exhibit haptic dominance during object size perception, even when auditory or visual information is available. The neural mechanisms subtending this process, however, were still unknown and are investigated here. Furthermore, this study serves the purpose of establishing a method that allows to assess the neural correlates of multisensory object size perception using active touch which will be further used in Chapter 4. The majority of studies that assessed the neural correlates of multisensory perception have done so under strictly controlled laboratory conditions using passive stimulation paradigms, either combining audio-visual, audio-tactile, or visuo-tactile stimuli. However, despite the clear advantages provided by high levels of experimental control, these methods neglect the active nature of perception. Therefore, this study provides a proof of concept for measuring neural markers of multisensory processing using active touch.

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Candidate's contribution to the paper (provide details, and also indicate as a percentage)	This study was a collaborative work between 5 authors at the University of Bath and University College London. Meike Scheller's contribution (30%) was related to the data analysis (40%) and the presentation of the study and associated data in journal format (65%). She further presented associated content at academic conferences.								
Statement from Candidate	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature.								
Signed	M.Scheller	Date	09.09.2019						

Active touch facilitates object size perception in children but not adults: a multisensory event related potential study

Meike Scheller^{a^}, Sara Garcia^{c^}, Joe Bathelt^b, Michelle de Haan^{c*}, Karin Petrini^{a*}

^a Department of Psychology, University of Bath, UK; ^b Brain & Cognition, University of Amsterdam,

Netherlands; ^c UCL Great Ormond Street Institute of Child Health, UK

^MS and SG are joint first authors, *KP and MDH are joint senior authors on this work.

Corresponding author:

Meike Scheller, Department of Psychology University of Bath Claverton Down, BA2 7AY Bath, United Kingdom e-mail: m.scheller@bath.ac.uk

Abstract

In order to increase perceptual precision the adult brain dynamically combines redundant information from different senses depending on their reliability. During object size estimation, for example, visual, auditory and haptic information can be integrated to increase the precision of the final size estimate. Young children, however, do not integrate sensory information optimally and instead rely on active touch. Whether this early haptic dominance is reflected in age-related differences in neural mechanisms and whether it is driven by changes in bottom-up perceptual or top-down attentional processes has not yet been investigated. Here, we recorded event-relatedpotentials from a group of adults and children aged 5-7 years during an object size perception task using auditory, visual and haptic information. Multisensory information was presented either congruently (conveying the same information) or incongruently (conflicting information). No behavioral responses were required from participants. When haptic size information was available via actively tapping the objects, response amplitudes in the mid-parietal area were significantly reduced by information congruency in children but not in adults between 190ms-250ms and 310ms- 370ms. These findings indicate that during object size perception only children's brain activity is modulated by active touch supporting a neural maturational shift from sensory dominance in early childhood to optimal multisensory benefit in adulthood.

Keywords: Sensory dominance, active touch, multisensory, event-related potentials, congruency, development

1. Introduction

Evidence suggests that the integration of multisensory information benefits perception by providing increased precision and accuracy in a multitude of everyday tasks (e.g. from object recognition to way finding; Ernst & Banks, 2002; Landy, Banks, & Knill, 2012). Contemporary work on the development of this process, however, has shown that children up until the age of 10-12 years, do not use multisensory information in the same way adults do, but rather rely dominantly on the sense that is more robust for the task at hand (Adams, 2016; Gori, Del Viva, Sandini, & Burr, 2008; Nardini, Jones, Bedford, & Braddick, 2008; Petrini, Remark, Smith, & Nardini, 2014). For example, Gori and colleagues (2008) asked adults and 5-10 year-old children to discriminate between the orientation and size of objects using either touch, vision, or both at the same time. They found that, while adults integrated haptic and visual information in a statistically optimal fashion, children focused predominantly on one sense, while almost completely ignoring information from the other sense (Gori et al., 2008). That is, during orientation discrimination children focused mostly on vision, while size discrimination was dominated by active touch. This haptic dominance during size discrimination has further been replicated using auditory and haptic cues (Petrini et al., 2014). Nevertheless, the reasons for the late development of adult-like multisensory integration and the long persistence of haptic dominance in childhood are poorly understood. Investigating how the temporal processing of ecologically relevant information changes throughout childhood can provide insights into the extent to which multisensory perceptual mechanisms rely on top-down attentional control, or the developmental maturation of the neural basis of low-level perception.

Up to now, few studies have examined the neural mechanisms of multisensory processing during development (e.g. Brandwein et al., 2011; Brett-Green, Miller, Gavin, & Davies, 2008; Johannsen & Röder, 2014) and even fewer studies have focused on somatosensory-auditory integration (Brett-Green et al., 2008). For example, using an event related potential (ERP) paradigm, Brandwein et al. (2011) investigated the developmental trajectory of neural processing of audio-visual information in children aged 7-16 years. They found that, behaviourally, children's integration performance gradually changed and reached mature levels at around 15 years of age, while the neural correlates for mature integration could already be detected at around 10-11 years. A systematic relationship between age and the brain processes underlying audio-visual integration was revealed in

the auditory N1 component (~120 ms), with the audio-visual peak amplitude changing from being more positive than the sum of visual and auditory amplitudes in 7-9 year-olds to being more negative than the sum of the visual and auditory amplitude in adults. In contrast, Brett-Green et al. (2008) found somatosensory-auditory integration effects in the signal amplitude of the P1-N1-P2 ERP complex in children aged 6-13 years, similar to what has previously been reported in adults (Foxe et al., 2000; Murray et al., 2005). In their sample they did, however, not differentiate between age-groups of children, thus leaving unclear whether there were developmental changes between 6 and 13 years old.

These developmental studies, as well as the few auditory-somatosensory studies in adults, suggest that the neurophysiological benefit driven by multisensory integration can be detected already at early stages of sensory processing (<150ms), which is characteristic of low-level or bottom-up mechanisms (De Meo, Murray, Clarke, & Matusz, 2015). This evidence, however, has been obtained in either audio-visual studies (e.g. Brandwein et al., 2011; De Meo et al., 2015) or studies using passive tactile stimuli (e.g. Brett-Green et al., 2008; Foxe et al., 2000; Sperdin, Cappe, Foxe, & Murray, 2009) so it is yet to be examined at which processing stage haptic dominance arises. As active touch requires cognitive control and attentional resources due to its goal-directed nature (De Meo et al., 2015) it could be largely influenced by top-down processes and detectable only at a later stage of processing.

Given the consistent findings indicating a dominance of active touch over both audition and vision during object size discrimination in childhood (Gori et al., 2008; Petrini et al., 2014), this study focuses on the mechanisms of haptic dominance using an ERP paradigm to measure sensory processing. Our investigation focuses specifically on mid-parietal regions because this area is known to play an important role in the integration of multisensory information. Previous findings have shown that both children and adults exhibit differences in the P1-N1-P2 components between simultaneous auditorysomatosensory responses and summed unisensory responses in midline and central/postcentral scalp regions (Brett-Green et al., 2008; Foxe et al., 2000; Murray et al., 2005). Furthermore, consistent developmental differences have previously been shown in parietal regions in multisensory ERP studies (Brandwein et al., 2011; Johannsen & Röder, 2014). These consistent developmental differences over parietal channels may indicate a critical role of the intraparietal sulcus (IPS), which has been identified as one of the areas classically associated with multisensory processing of tactile, auditory and visual information (e.g. Ben Hamed, Duhamel, Bremmer, & Graf, 2001; Saito, Okada, Morita, Yonekura, & Sadato, 2003; Stilla & Sathian, 2008).

To investigate the modulatory effect of active touch on object size perception, we adapted the task of Petrini et al. (2014) and presented two balls of different size in either audioonly, audio-visual, or audio-visual-haptic condition while manipulating the size information congruency between these different sensory modalities. That is, we used multisensory incongruency as an indicator of object size consistency among the senses and predicted that children would show a larger difference in ERP amplitude than adults for congruent and incongruent haptic information, given children's higher reliance on active touch. We expected to find a larger effect of haptic congruency in children when compared to adults given the commonly found effect of multisensory integration (e.g. Brandwein et al., 2011; Brett-Green et al., 2008; Foxe et al., 2000; Murray et al., 2005). We further hypothesized that we would find a differential activation in the N2 component, given that our paradigm introduced a multisensory conflict, which has repeatedly been shown to modulate this component in adults (Forster & Pavone, 2008; Gu, Mai, & Luo, 2013; Lindström, Paavilainen, Kujala, & Tervaniemi, 2012; Lu, Ho, Sun, Johnson, & Thompson, 2016).

2. Methods

4.1 Participants

10 children aged between 5 and 7 years (M = 6, SD = 0.82; 4 female) and 10 adults aged between 20 and 31 years (M = 23.9, SD = 3.57; 6 female) participated. This sample size was calculated for a Cohen's F effect size equal to 0.5 through a priori type of power analysis for an ANOVA repeated measures within-between interactions. We used G*Power 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007) and assumed a level of power of 0.80, with 2 groups, 3 measurements, and an alpha level of 0.05. The age range for the recruited children was based on the behavioral evidence that children younger than 8 years do not integrate haptic information with either vision and sound but instead show a strong dominance of the haptic information when perceiving and judging object size (Gori et al., 2008; Petrini et al., 2014). The number of participants is similar to the previous developmental ERP study using passive tactile stimulation to investigate

somatosensory-auditory integration (Brett-Green et al., 2008). There was one left handed person in the adult group and two in the group of children as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). The remaining participants were either ambidextrous with a preference for using the right hand or fully right-handed. Ethics permission was granted by the UCL Great Ormond Street Institute of Child Health Research ethics committee (02CN01).

4.2. Stimuli

Visual and haptic stimuli were two wooden balls (see Figure 1), a big ball (57mm diameter) and a small ball (41mm diameter). The corresponding sound amplitude for the big ball was 79dB and for the small ball was 71dB. The stimuli for the visual, haptic and auditory modalities were selected from a set of balls and corresponding sounds previously used and tested by Petrini et al. (2014). The two ball and corresponding sound sizes used here were at the ends of the range used in Petrini et al. (2014) and were easily perceived as different in size by two separate samples of children and adults of the same age of the participants taking part to this study (see Figure 2 in Petrini et al., 2014). The reason for selecting two balls and sounds that could be easily differentiated based on size (i.e. through differences in height for touch and loudness for sound) is so that we could be sure all participants perceived the difference in size with touch and sound without the need of asking for behavioral responses. We opted not to assess behavioral responses based on a relevant previous developmental study examining the integration of somatosensory and sound information (Brett-Green et al., 2008). Sound recordings lasted for 66ms.



Figure 1. The two balls used as stimuli in the study.

4.3. Procedure

Participants were seated comfortably and asked to rest their dominant hand on a rectangular (5cm deep) semi-soft foam surface, covering a (Touch ProE-X, Keytech Inc Magic, Texas, USA) touch screen, positioned before them on a table. A speaker (Logitech, Lausanne, Switzerland) was positioned directly below the touch screen, underneath the table, hidden from view (see Figure 2). Randomization of condition order and stimuli presentation were controlled using Matlab (Version R2014a, The MathWorks Inc., Natick, MA) and the Psychophysics toolbox extensions (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997), on a Dell computer running Windows XP Service Pack 3 (Microsoft Inc., NW).



Figure 2. Sketch of the experimental setup and the three conditions. Upper panel shows the experimenter (left) and participant (right) interacting with the stimuli in the audio-visual- haptic condition. Here, the participant was tapping the wooden ball while looking at it. A sound was played in response to the tap from a speaker positioned out of view from right underneath the setup. Lower panel shows a sketch of the three conditions including the participant listening to the sound alone (audio), listening to the sound while observing the experimenter tapping the ball (audio-visual), and the sound paired with seeing and tapping the ball themselves (audio-visual-haptic)

Before the experiment started participants were shown the two balls and they all easily identified the smaller and bigger ball. Participants completed five blocks (see Table 1) of 48 trials with a short break after each set of 6 trials. The trials were started manually as in Petrini et al. (2014). That means that the time between trials was variable. We used unpredictable interval to minimise expectation effects as suggested by Woodman (2010) to avoid that the alpha-wave activity of participants became phase locked with the stimulus presentation rate. Also, we triggered the onset of the next trial manually to ensure that all participants were paying attention when the stimulus was presented. During the experiment, participants were asked to look at a square hole that had been cut in the middle of the rectangular foam surface on which their hand was rested. The experimenter monitored the participant's attention by making sure that participants kept looking at the square hole at all time during the block. The experimenter (but not the participant) was able to look at changes in looking behavior thanks to a video recording of the participant shown on the computer. During 'audio' blocks, participants were asked to listen to the ball sounds that were triggered by the experimenter pressing a mouse button. Here, the only information about object size that participants received was auditory (either the sound of the small ball or of the big ball). During 'audio-visual' blocks, the experimenter placed one of the wooden balls within the square hole, and participants were asked to observe the experimenter tap the ball. The tap elicited pressure on the touch screen which triggered the sound to be played back instantaneously. During 'audio-visual-haptic' blocks, the experimenter placed the ball inside the square hole and asked the participant to tap the ball themselves. Thereby, participants were instructed to keep their hand straight and flat during the tapping movement in order to minimize any effects that might result from differences in hand sizes between adults and children (as in Petrini et al., 2014). That is, as adults have larger hands, curving the hand would allow them to assess more information than children. Keeping the hand straight and flat was supposed to control for such differences. Once the ball was tapped and pressure was sensed on the touch screen, the sound recording was played. This sound was either congruent (e.g. 41mm ball and 71dB sound) or incongruent (e.g. 41mm ball and 79dB sound) with the size information delivered by haptic and visual modalities. The visual information (the visible action of tapping the ball) was kept as similar as possible in the audio-visual and audio-visual-haptic condition by positioning the experimenter on the same side of the arm used by the participant. A thin 1cm layer of soft foam was inserted between the thick layer of foam and the touch screen positioned underneath to eliminate

any impact sound between the wooden balls and the hard surface of the touch screen). The visual stimulation persisted longer than the sound of the ball hitting the surface. Participants were instructed to close their eyes while the experimenter was positioning the ball in the square hole of the soft foam surface. Participants were then allowed to look at the ball and either tap it themselves (audio-visual-haptic condition) or observe the experimenter tapping the ball (audio-visual condition). The sound was triggered by the haptic tap without time delays.

Table	1.	Ex	perimental	design

Block	Person tapping	Ball tapped	Auditory Stimuli
Audio	None	None	small, big
Audio-visual	Experimenter	Small	small, big (congruent/incongruent)
Audio-visual-haptic	Participant	Small	small, big (congruent/incongruent)
Audio-visual	Experimenter	Big	small, big, (incongruent/congruent)
Audio-visual-haptic	Participant	Big	small, big (incongruent/congruent)

4.1 Data acquisition

The EEG was recorded using a GES 200 high-density, high-impedance recording system, a NetAmps 200 amplifier and HydroCel Geodesic Sensor Nets with 128 channels (Electrical Geodesics Inc., OR). Recordings were obtained using NetStation software V4.1.2 (Electrical Geodesics Inc., OR) on an Apple Macintosh PowerPC G4 running Mac OS 10.3.9. The sample frequency was set to 250Hz. A vertex reference was used for recording.

The amplifier was calibrated and impedances were measured before each recording. Channels with impedance higher than $501 < \Omega$ were checked for good contact with the scalp and adjusted where necessary. An event code was sent to NetStation via Matlab whenever an auditory stimulus was triggered.

4.5 EEG Processing and Analysis

Due to an error during recording (a failed communication between NetStation and

Matlab), the EEG was not recorded for trials in which the big ball was tapped (the data for these trials were not saved), therefore only the EEG for trials in which the small ball was tapped with either the small ball (congruent condition) or big ball (incongruent condition) sound were included in the analyses. Not including the data for the tapped big ball did not affect the data for the tapped small ball as these two conditions were carried out separately. The EEG signal was filtered off-line using a 0.1Hz high-pass filter and 30Hz low-pass filter. The ERP is dominated by lower EEG frequencies. Higher frequencies are less relevant for the ERP and may be contaminated by high frequency noise, such as muscle artefacts. A low-pass filter at 30Hz is therefore routinely applied across many studies. The high-pass filter was applied to remove low-frequency drift associated with electrode shearing or drying, and 0.1 Hz is what is recommended when testing children (Acunzo, Mackenzie, & van Rossum, 2012). Channels with weak correlation (r < 0.3) to neighboring channels were removed. Timing tests indicated a 24ms delay between stimulus trigger (haptic tap) and sound presentation. ERPs were time-locked to the sound. This delay was systematically adjusted for every logged event presentation. EEG recordings were then segmented into 650ms epochs, starting at -50ms before the trigger until 600ms following the trigger. For each segment, channels with a peak-to-peak amplitude larger than 80µv were replaced using spherical interpolation of neighboring channel values using EEGLAB v13.2.1 functions. The spherical interpolation is the recommended and default approach to replace noisy electrodes in EEGLAB. This method provides the most accurate interpolation for high- density EEG (Perrin, Pernier, Bertrand, & Echallier, 1989). Any segments for which 30% of all channels exceeded 100µv were excluded. The EEG was re-referenced to the average reference, with eye channels being excluded. Baseline correction was applied for a short temporal window of 10ms-20ms post-stimulus. This temporal window was chosen in order to avoid incorporating movement artifacts that result from arm movements during the audio-visual-haptic condition into the baseline correction and is in line with previous research investigating multisensory integration of audio-somatosensory stimuli (Foxe et al., 2000). Segmented trials were submitted to an Independent Component Analysis (ICA). A kurtosis threshold of 3 was used to detect unusually peaky activity distributions which are likely to represent artifacts (Delorme, Sejnowski, & Makeig, 2007), and were consequently removed. Following artifact rejection, an average was computed for each participant for each condition. Children retained, on average, 12 audio-big, 18 audiosmall, 14 audio-visual-incongruent, 14 audio-visual-congruent, 14 audio-visual-hapticincongruent, and 14 audio-visual-haptic-congruent trials. Adults retained, on average, 22 audio-big, 24 audio-small, 24 audio-visual-incongruent, 24 audio-visual-congruent, 23 audio- visual-haptic-incongruent and 23 audio-visual-haptic-congruent trials.

Individual artifact-free trials were combined to individual averages for each condition, upon which grand-average waveforms for each condition were computed, including all participants in both age groups. Difference waves based on the congruency of the stimuli were calculated for each multisensory condition and each individual by subtracting responses to congruent stimuli from responses to incongruent stimuli. Only the size information of the modality of interest (e.g. haptic) differed between the congruent and incongruent condition. Grand averages of the difference waves were computed for both the adult and children group. As we used three different modes of stimulus presentation (audio, audio + visual, and audio + visual + active touch) we could not directly compare between these conditions. This is because the three conditions differ in the amount of muscle movement (noise). In order to allow for a comparison between these conditions, we made use of the sensory congruency effect by testing congruent vs incongruent stimulus pairs, and then looked at these congruency effects in the three conditions. As the amount of movement was different between the A, AV, AVH conditions, but not between congruent and incongruent stimulus pairs within each of these conditions, we were able to compare whether the neural response to the congruency between the two stimuli differs when touch is available (AVH), compared to when is not available (AV).

The difference waves reported here indicate the subtracted potential of incongruent from congruent responses. Basically, what this allows us to do is to subtract the activity from other processes that are similar between congruent/incongruent conditions (e.g. noise due to arm movements/motor planning activity in AVH), and hence are not related to perceiving the object's size based on congruent multisensory information. For direct comparison between similar conditions (that only vary by one factor, in our case congruency), difference waves calculation is recommended (Kappenman & Luck, 2016).

In order to identify the temporal onset of processing differences, time windows that showed significantly different responses between congruent and incongruent information processing were defined. For that purpose, the difference potentials were segmented into 163 discrete time points across the whole duration of the segment from -50 ms to 600 ms. For each time point a paired comparison (paired *t*-test) of the difference wave amplitude and 0 was conducted. In order to control for an inflation of alpha error, we estimated the sequence length that was necessary to indicate significant deviations from 0. That is, deviations would only be deemed significant if a sequence of twelve or more consecutive time points (equal to 46 ms) would yield statistically significant results (see Guthrie and Buchwald, 1991). This method is an alternative to a traditional Bonferroni-correction that takes the spatio-temporal dependence of neural signals into account. It has been developed by Guthrie and Buchwald (1991) specifically for the analysis of difference potentials and has been used in previous multisensory studies (e.g. Butler, Foxe, Fiebelkorn, Mercier, and Molholm, 2012; Stekelenburg and Vroomen, 2007). The amount of consecutive time points (i.e. twelve in our case) depends on the amount of comparisons made for each difference wave (i.e. how many time points are compared), autocorrelation in the data, and the number of subjects. We calculated the amount of consecutive time points for both adults and children separately.

We focused on mid-parietal channels based on previous findings showing alterations in early-latency signals between simultaneous auditory-somatosensory responses and summed unisensory responses at midline and central/post-central scalp regions (Brett-Green et al., 2008; Foxe et al., 2000; Murray et al., 2005). Furthermore, several multisensory ERP studies have shown consistent developmental differences in the parietal region (Brandwein et al., 2011; Johannsen & Röder, 2014). The EEG, however, was recorded with standard nets that contained 128 electrodes. The high density of electrodes has several advantages that were exploited in the current analysis. First, all electrodes were used for the analysis to calculate the average reference. This is the closest possible approximation to a reference-free recording (Nunez & Srinivasan, 2006). Second, each position in the 10-20 system is covered by several electrodes so that an average signal can be calculated that is less influenced by noise that may affect individual electrodes. Further, the high-density of electrodes provides better spatial information about the topography of the ERP. The main statistical comparison focused on channel regions that were indicated based on previous studies. The other electrodes were not excluded but were not of primary interest for the analysis.

We furthermore employed a component-based analysis to assess the effects of age and condition on four different ERP components: N1, P2, N2, and P3. Visual inspection of the waveforms and topographic maps indicated the presence of the N1-P2 complex, followed by a negative deflection (N2), and a positive wave (P3) at midline parietal sites. This sequence of components is in line with previous reports using similar paradigms (Brandwein et al., 2011; Brett-Green et al., 2008). Area amplitudes and mid-area latencies were computed for the average ERP at mid-parietal channels, at each of the component time windows identified. Area amplitudes are the absolute cumulative areas between baseline and signal amplitude. Mid-area latencies are the time points that divided the area amplitudes into equal fractions and has been found to provide a more reliable timing measure than peak latency (Kiesel, Miller, Jolicœur, & Brisson, 2008; Luck, 2005). For each condition (audio, audio-visual, audio-visual-haptic), repeated measures analysis of variance (ANOVA) models with congruency (congruent, incongruent) as the withinsubjects factor and participant group (adults, children) as the between-subjects factor were used to compare latencies and amplitudes between groups. As there were no differences between peak and area measures (see tables in Appendix), we only reported the area-based ERP measures, since these are the most robust against increases in background noise (Clayson, Baldwin, & Larson, 2013). Mid-parietal channels were chosen based on previous findings showing alterations in early-latency signals between simultaneous auditory-somatosensory responses and summed unisensory responses at midline and central/post-central scalp regions (Brett-Green et al., 2008; Foxe et al., 2000; Murray et al., 2005). Furthermore, several multisensory ERP studies have shown consistent developmental differences in the parietal region (Brandwein et al., 2011; Johannsen & Röder, 2014).

3. Results

Figure 3 shows the grand average ERPs for audio, audio-visual and audio-visual-haptic conditions for mid-parietal channels (61, 62, 67, 72, 77, 78). Children showed overall higher responses than adults. Difference waves between responses to congruent and incongruent stimuli were calculated for both adults and children (see left panels in Figure 4). Please see the supplemental material for a component-based analysis returning similar results.



Figure 3: Grand average event related potentials (ERPs) for auditory (black), audiovisual (blue) and audio-visual-haptic (red) conditions, at midline-parietal channels for adults (top three panels) and children (bottom three panels). Time 0 represents the onset of the auditory stimulus. Shaded error bands around the means represent the standard error. Note that the response to the auditory stimulus is plotted in both, the congruent and incongruent response plots to serve as a reference.

Data-driven time window estimation

ERP difference waves based on comparison between congruent and incongruent trials showed a significant deviation from 0 for latencies between 190ms-250ms (p < .05 for 16 consecutive time points) and 310ms-370ms (p < .05 for 16 consecutive time points). However, this was only true for children in the audio-visual-haptic condition and not for the audio-visual condition, or for adults (see Figure 4, left panels). Scalp topography plots show activity to audio-visual-haptic stimulus presentation occurred primarily in posterior areas (right panels).



Figure 4: Difference waves for the audio-visual and audio-visual-haptic conditions for adults (top panel) and children (lower panel). Time windows for which significant deviations from 0 exist in the audio-visual haptic condition are shaded in grey. Scalp topographies are displayed for the mean activity at mid-latency of the two time windows that were identified (190ms-250ms, 310ms-370ms) for both age groups.

Area amplitude

Age group showed significant differences in area amplitude for all components in all conditions, with children exhibiting greater area amplitudes overall (see Table 2, Figure 5).

In the audio-only condition, there was no effect of ball size, and no ball size by group interaction ($F_{[1,18]} = 5.74$, p = 0.028, $\eta^2 = 0.04$; see Table 2), except for the P3 component. Here, adult ERPs tended to show greater area amplitudes for the big ball ($t_{[9]} = 2.151$, p = 0.060, d = 1.56), while child ERPs tended to show greater area amplitudes for the small ball ($t_{[9]} = 1.504$, p = 0.167, d = 0.41, Figure 5).

For audio-visual stimulus presentation, there was no effect of congruency, however there was a significant congruency by group interaction for the P2 component ($F_{[1,18]} = 5.146$, p = 0.036, $\eta^2 = 0.09$; see Table 2). This interaction was driven by children's ERPs tending to show greater area amplitude in the incongruent conditions ($t_{[9]} = 1.816$, p = 0.103, d = 1.63), whereas adults' ERPs tended to show greater area amplitude in the congruent conditions ($t_{[9]} = 1.450$, p = 0.181, d = 0.46; Figure 5).

During audio-visual-haptic stimulus perception, the N2 component was significantly modulated by congruency ($F_{[1,18]} = 10.57$., p = 0.004, $\eta^2 = 0.02$; see Table 2), showing greater area amplitudes for the incongruent condition. However, this modulation was largely driven by the children's responses. This was also reflected by a significant congruency by group interaction, both for the P2 ($F_{[1,18]} = 4.541$, p = 0.047, $\eta^2 = 0.05$) and N2 ($F_{[1,18]} = 9.623$., p = 0.006, $\eta^2 = 0.02$) components. Here, children exhibited greater area amplitudes in incongruent than congruent conditions (P2: $t_{[9]} = 2.046$, p = 0.071, d = 0.93; N2: $t_{[9]} = 3.989$, p = 0.003, d = 0.5), whereas adults showed similar area amplitudes in congruent conditions (P2: $t_{[9]} = 0.630$, p = 0.544, d = 0.14; N2: $t_{[9]} = 0.123$, p = 0.905, d = 0.03; Figure 5).



Figure 5. Mean area amplitude activation within components N1, P2, N2 and P3 during incongruent and congruent cue presentation, shown for both multimodal conditions; audio-visual and audio-visual-haptic. Children's data are indicated by empty circles and dashed line, adult data is shown by solid line and filled circles.

Table 2. ANOVA test statistics for effects of age group and condition effects on ERP mean area amplitude. Conditions differ between ball sizes for audio-only trials, and congruency for multisensory trials. * indicate statistical significance (with $\alpha = .05$)

		Main effect: group			Main effect: conditions (ball size/congruency)			Interaction		
Sensory condition	Component	F [1,18]	p-value	η^2	F [1,18]	p-value	η^2	F [1,18]	p-value	η^2
	N1	6.627	0.019*	0.216	1.507	0.235	0.015	1.507	0.235	0.004
Audio	P2	5.030	0.038*	0.107	3.314	0.085	0.077	0.660	0.427	0.015
	N2	11.623	0.003*	0.242	1.721	0.206	0.033	0.433	0.519	0.008
	P3	25.155	<.001*	0.479	0.034	0.856	<.001	5.740	0.028*	0.043
	N1	9.578	0.006*	0.268	1,263	0.276	0.015	0.657	0.428	0.008
Audio-	P2	12.689	0.002*	0.235	0.992	0.333	0.018	5.146	0.036*	0.092
visual	N2	7.707	0.012*	0.168	0.114	0.740	0.003	0.377	0.547	0.009
	P3	8.090	0.011*	0.191	0.564	0.462	0.011	0.405	0.553	0.008
	N1	13.199	0.002*	0.316	<.001	>.999	<.001	1.901	0.185	0.024
Audio-	P2	11.951	0.003*	0.297	2.717	0.117	0.028	4.541	0.047*	0.046
visual-	N2	10.876	0.004*	0.344	10.570	0.004*	0.024	9.623	0.006*	0.022
haptic	P3	12.243	0.003*	0.016	3.885	0.064	0.025	2.454	0.135	0.016

Mid-area latency

There were no significant main effects of age group or ball size on mid-area latencies when sound was presented alone. There was also no significant ball size by group interaction. In the audio-visual condition, there was no significant effect of age group or congruency on mid-area latencies and no significant interactions between the two factors. Finally, no significant main effect of group or congruency and no interaction effect on mid-area latencies in the audio-visual-haptic condition were found (see Table 3).

Table 3. ANOVA test statistics for effects of age group and condition effects on ERP mid-area latency. Conditions differ between ball sizes for audio-only trials, and congruency for multisensory trials.

		Main ef	fect: grou	ıp	Main ef (ball siz	ffect: cond æ/congrue	conditions Interaction ngruency)			
Sensory Condition	Component	F [1,18]	p- value	η^2	F [1,18]	p- value	η^2	F [1,18]	p- value	η²
	N1	0.065	0.801	0.001	0.003	0.954	<.001	0.165	0.689	0.006
Audio	P2	0.831	0.374	0.029	0.044	0.835	<.001	2.614	0.123	0.043
	N2	1.225	0.283	0.034	3.830	0.066	0.07	3.830	0.066	0.07
	P3	2.362	0.142	0.055	0.071	0.793	0.002	3.466	0.079	0.084
	N1	0.025	0.877	<.001	0.139	0.713	0.003	1.706	0.208	0.038
Audio-	P2	0.737	0.402	0.02	1.762	0.201	0.043	0.261	0.616	0.006
visual	N2	0.385	0.543	0.015	0.041	0.842	<.001	0.041	0.842	<.001
	P3	1.453	0.244	0.043	0.038	0.848	<.001	0.152	0.702	0.004
	N1	0.044	0.836	0.002	0.448	0.512	0.009	0.740	0.401	0.014
Audio-	P2	0.941	0.345	0.035	3.014	0.100	0.041	0.753	0.397	0.01
visual-	N2	0.130	0.722	0.005	1.688	0.210	0.025	0.126	0.727	0.002
haptic	P3	0.384	0.543	0.013	0.659	0.428	0.013	0.384	0.543	0.035

In summary, there were no differences in the mid-area latencies of ERP components between adults and children. However, area amplitudes were significantly larger in children than adults across all conditions (audio, audio-visual, audio-visual-haptic). Moreover, there was a significant effect of congruency on the area amplitude of the N2 component, and a significant group by congruency interaction for the area amplitude of both the P2 and N2 components (see Table 2 and Figure 5). However, the significant interaction between age group and congruency was specific to the AVH condition (as there was no such a significant interaction for the AV condition), while the interaction between age group and congruency found for P2 was significant for both AV and AVH conditions.

3. Discussion

Combining different senses can reduce uncertainty in everyday tasks and thus improve our precision. Whilst adults can integrate different sensory information optimally by weighting it based on the reliability of each sensory modality, children younger than 8 years generally do not behave optimally. For example, children do not integrate active touch with either sound or vision optimally when perceiving and judging objects' sizes, but show a strong dominance of the haptic information (Gori et al., 2008; Petrini et al., 2014). Whereas previous studies have examined the development of multisensory integration in childhood using electrophysiological methods and passive tactile stimulation (e.g. Brandwein et al., 2011; Brett-Green et al., 2008), it is not yet known how sensory dominance of active touch is reflected in neurophysiological differences between young children and adults. Furthermore, whilst evidence suggests that sub- or super-additive multisensory integration can occur already at early stages of processing (<150ms; e.g. Brett-Green et al., 2008; De Meo et al., 2015; Foxe et al., 2000; Sperdin et al., 2009), it is unknown whether sensory dominance arises at such early stages of processing as well.

Our results revealed a reduction in amplitude during time windows that are temporally aligned with the N2 (190ms-250ms) and the P3b (310ms-370ms) component in midparietal regions for children but not for adults. However, this was only the case when haptic congruent information about the object size was available. Interestingly, this reduction in amplitude was not evident when congruent auditory and visual information were presented alone.

We predicted a modulation of the N2 component based on several ERP studies reporting its sensitivity towards multisensory conflict. For example, response amplitudes to multisensory stimuli that were incongruent in spatial location, temporal synchrony, direction of movement, or emotional content have been found to be larger with respect to congruent pairings (Forster & Pavone, 2008; Gu et al., 2013; Lindström et al., 2012; Lu et al., 2016; Nieuwenhuis et al., 2003). The findings of the current study confirm this directionality of amplitude modulation as children showed a larger amplitude in the audio-visual-haptic incongruent than congruent condition in a time window and channel region that are consistent with the N2 component. Neural processing changes in the parietal region in children may indicate a critical role of the intraparietal sulcus (IPS), which has been consistently associated with multisensory processing (Bolognini & Maravita, 2007; Kamke, Vieth, Cottrell, & Mattingley, 2012; Sereno & Huang, 2014). Furthermore, the IPS has been shown to play a crucial role in global object perception (Amedi, von Kriegstein, van Atteveldt, Beauchamp, & Naumer, 2005; Bodegård, Geyer, Grefkes, Zilles, & Roland, 2001; Faillenot, Decety, & Jeannerod, 1999; Roland, O'Sullivan, & Kawashima, 1998; Sathian et al., 2011) and the on-line adjustment of monitoring and adjusting grasping movements to object size (Glover, Miall, & Rushworth, 2005). However, we cannot be sure about the exact generators, which should be investigated in future study with a larger sample size and a higher spatial resolution.

In contrast to children, adults did not show a congruency-dependent modulation of the N2. This result may indicate that children younger than 8 years have a higher sensitivity to multisensory conflict when active touch is involved as compared to adults. The reason why adults do not show such modulation may result from a stronger weighting of auditory information when judging object size that is reflected by a significantly higher precision in sound discrimination (Petrini et al., 2014). As shown in previous studies assessing attentional modulation of cross-modal interactions in adults, touch, in comparison to vision or audition, possesses a special role because it can be decoupled from the other senses (Eimer, Van Velzen, & Driver, 2002). That is, while auditory and visual cueing influence sensory processing in the respective other sense, touch does not bias sensory processing in either visual (Eimer & Driver, 2000) nor auditory (Eimer et al., 2002) attended cues. Hence, as the ability to use sound is greater in adults than children when estimating object size, adults may have ignored or decoupled haptic information while children may have been unable to ignore such information. This is also supported by research showing that children are often unable to ignore irrelevant sensory information (Innes-Brown et al., 2011; Petrini, Jones, Smith, & Nardini, 2015).

We further found a significant difference between responses to congruent and incongruent stimuli in children in the audio-visual-haptic condition during a later time window (310ms-370ms) that we did not predict. The latencies and parietal distribution response difference are associated with the conflict-sensitive P3b, a subcomponent of the P300 component (Polich, 2004). This subcomponent has been shown to be involved in memory processing (Polich, 2007) and visuo-motor learning (Morgan, Luu, & Tucker, 2016). It has further been shown to be modulated by levels of expertise (Morgan et al.,

2016) which could explain why, in the present study, we found differences between children and adults in this component.

Contrary to our expectation, we did not find any age-related modulation of the N1 when active touch was involved. This suggests that haptic dominance in children does not arise at earlier stages (<150ms) of processing but rather at later stages (De Meo et al., 2015) and might therefore be modulated by top-down processes. This difference between our results and those of studies reporting earlier occurrences of somatosensory-auditory integration (e.g. Brett-Green et al., 2008; Foxe et al., 2000; Sperdin et al., 2009) may be explained by the use of active touch instead of passive tactile stimulation. Given that active touch is usually goal-directed and thus requires motor planning and attentional control, latency differences between somatosensory and haptic information processing would not be surprising. Therefore, this later influence of haptic dominance on sensory processing may not be generalizable to other multisensory dominance processes that do not involve goal-directed actions. ERP developmental studies of action monitoring and cognitive control do show a modulation of N2 component for congruent and incongruent stimuli (e.g. Ladouceur, Dahl, Carter, 2004, 2007; Buss et al., 2011) similarly to our study, with incongruent stimuli inducing a larger N2 response than congruent stimuli. However, these studies show an increase in N2 or N2 difference waves response with age rather than a decrease in this component as we have shown here. Hence, our results cannot be fully explained by age-related changes in cognitive control or action monitoring. A possible explanation of why our results differ from those of the aforementioned studies is that our participants did not perform a task as we did not want to assess the effect of error monitoring performance in children and adults (e.g. Ladouceur, Dahl, Carter, 2004, 2007; Buss et al., 2011) but rather the age-related effect of active touch on object perception. Future research could further examine whether the involvement of top-down control over sensory dominance is essential or whether sensory dominance as assessed with passive multisensory stimulation is a purely perceptual mechanism.

Our results are in agreement with the few multisensory developmental studies using neurophysiological measures that show a change in multisensory processing from early childhood to adulthood. In the study by Brandwein and colleagues (2011), a clear developmental change in response amplitude was shown within a time window ~100ms-140ms as well as in the parietal region between 190ms and 240ms (see Figure 9 in

Brandwein et al. 2011). The amplitude of the audio-visual response was less negative than the sum of the auditory and visual responses in younger children (7-9-year-old), had the same level of negativity for the 10-12-year-old children, and became more negative than the auditory and visual sum for the older groups (13-16-year-old children and adults). This prolonged maturation of adult-like multisensory processing during childhood appears to be led by a prioritization of the unisensory process (Neil, Chee-Ruiter, Scheier, Lewkowicz, & Shimojo, 2006; Stein, Labos, & Kruger, 1973; Stein & Meredith, 1993; Wallace & Stein, 2001), which is not surprising given the many physical and physiological changes occurring in this developmental period (e.g. changes in structural and functional brain organization, physical changes in hand and body size, and maturation of the auditory cortex; Moore & Linthicum, 2007; Paus, 2005; Ponton, Eggermont, Kwong, & Don, 2000; Steinberg, 2005). In other words, before adult-like multisensory integration can be fully achieved, the individual senses need to stabilize through a cross-calibration process requiring the most reliable sense to teach the less reliable sense to accurately process the perceptual properties of objects in the environment (Gori et al., 2008). In the current study, we support this view by showing that in children, in contrast to adults, haptic information (known to dominate children's object size perception by calibrating vision and auditory information for object size judgment; Gori et al., 2008; Petrini et al., 2014) modulates the brain's response to visual and auditory information. Our support for the cross-calibration hypothesis (Gori et al., 2008), however, seems to be in contrast with recent findings showing a lack of motorsensory recalibration in children aged 8-11 years (Vercillo et al., 2014). While the development of recalibration (shift after adaptation to sensory asynchrony) and crosscalibration are probably linked, they are not the same mechanism as cross-modal calibration as discussed in our paper is a process by which the most robust sense for one task teaches the other senses so that accurate perception can be achieved. In Vercillo et al.'s (2014) study children did not show motorsensory recalibration probably because children have been shown by several studies to have lower sensitivity to multisensory asynchrony (i.e. bigger temporal integration/binding window: e.g. Stanley et al., 2019; Hillock-Dunn & Wallace, 2012; Hillock, Powers, & Wallace, 2011), that is, children, compared to adults, keep perceiving synchrony for larger delays between the senses and consequently may not recalibrate because they do not perceive the delay. In our study there was no variable motorsensory asynchrony, the only manipulation was in sensory congruency, which has been shown to affect children's as well as adults' performance
(Petrini et al., 2014) of the same age as tested in our study. Hence, while children may gain from cross-calibration, i.e. gain from the inclusion of the most robust sense for the task when perceiving an object, they may not recalibrate due to their lower sensitivity to asynchrony.

An alternative explanation of the age-related effect found here could refer to the mere differences in number of sensory cues in the audio-visual and audio-visual-haptic conditions, i.e. one condition has two sensory cues while the other has three. However, it is difficult to explain these findings based merely on the number of senses involved given that in adults the trimodal and bimodal conditions give rise to the same ERP results. This lack of difference between trimodal and bimodal conditions in the current study for the adult group stands in contrast to evidence showing that in adults trimodal conditions generate a multisensory advantage when compared to bimodal and unimodal conditions (e.g. Diederich & Colonius, 2004). Moreover, the effect is specific to the N2 component in children. If the number of senses was the main driver of the findings then it is unclear why both the audio-visual and audio-visual-haptic condition led to a decrease in amplitude for earlier components in children, despite the different number of cues. Thus, the dominance of haptic information for size perception in childhood appears to be a more plausible explanation for the findings. Nevertheless, future neurophysiological studies with adult participants could compare different bimodal combinations (audio-visual, audio-haptic, and visual-haptic) to a more naturalistic, multimodal (here trimodal) setting (e.g. audio-visual-haptic).

Despite our best efforts to match the visual information in AV and AVH these two visual conditions were not exactly the same. The only way they could have been matched perfectly while still keeping the task realistic (i.e. rather than using recorded videos for AV condition) was through immersive virtual reality. Unfortunately using the EEG cap with the head mounted display would have been problematic and would have added more noise to the data. However, given the progress made to integrate these technologies in recent years (e.g. Ehinger et al., 2014) it should be possible to overcome this limitation in future studies using a similar paradigm. Nevertheless, the component-based analysis does show similar results for AV and AVH in P2 which point to a similarity in processing of the two conditions. Finally, although the number of retained trials per participant was low, a recent paper has shown that the internal consistency of event-related potentials

associated with cognitive control in N2 and P3 can be achieved after 14-20 trials (Rietdijk et al., 2014). This together with the fact that both the component-based and difference waves analysis returned the same results indicate that our results are reliable despite the low number of trials.

Conclusion

Based on behavioural evidence it has been established that young children do not integrate active touch with either sound or vision when perceiving and judging objects' size but rather show a strong dominance of the haptic information (Gori et al., 2008; Petrini et al., 2014). To the best of our knowledge, however, the underlying changes in brain activity that may reflect this haptic dominance in early childhood have not been previously documented. Here, we used electrophysiology to examine the difference in brain processes between young children and adults when using active touch to perceive and judge object size. Our ERP data show a modulation of the neural response during two distinct time-windows that is aligned with the conflict-sensitive N2 and P3b components. This modulation is, however, only present in response to haptic in-/congruency in children, while it is not present in adults. This result is consistent with the behavioral data showing overreliance of children on haptic information aimed at facilitating the cross-sensory calibration needed to achieve an adult-like multisensory mechanism of object perception. This study is the first to use active touch in an ERP study to assess sensory dominance in young children and its results are an important benchmark against which to assess the development of this sensory developmental stage in different clinical and sensory impaired populations with known atypical multisensory processing (e.g. autism, schizophrenia, and individuals with visual, hearing, or motor impairments).

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In order to assess the neural markers of haptic dominance in children, we combined auditory, visual, and haptic information to assess whether children process multisensory congruency differently than adults, when haptic information is available. As the direct comparison of conditions (i.e. auditory, audio-visual, audio-visual-haptic) was not possible due to differences in the amount of sensory information across the conditions, as well as the combination of active and passive conditions, we made use of the brain's capacity to process sensory conflict (congruency). That is, by comparing audio-visual and audio-visual-haptic stimuli in either congruent or incongruent pairings, we showed that children process congruent and incongruent information differently only when active touch is present, but not when only audio-visual information was available. In adults, however, we did not observe a similar modulation in the presence of active touch.

The design of this study allowed us to provide the first evidence for neural processing of sensory dominance in sighted children and to test and refine the methodology for assessing optimal multisensory integration in a later study. We could show that event-related potentials can be reliably measured using active touch in a multisensory context, that is, together with visual and auditory information. Arguably, the different timing onsets between the stimuli might appear problematic, however, previous research showed that adding a second multisensory stimulus to an ongoing processing stream typically leads to an increase in neural activity within the other sense, likely through phase resetting in the ongoing oscillatory activity (Mercier et al., 2013; Naue et al., 2011). Hence, by time-locking the event-related potentials to the stimulus that was added last (sound) to the present and ongoing sensory processing stream (visual, haptic), the responses we measured originated from multisensory processing involving all three or two senses at the same time (audio-visual-haptic and visual-haptic conditions, respectively).

Overall, with this study we were able not only to show sensory dominance at the sensory level but also that the method of comparing multisensory size perception using active touch can be adapted to be used in an electrophysiological context. This allowed us to investigate the neural mechanisms of multisensory integration in sighted and non-sighted individuals, which is presented in Chapter 4.

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Chapter 3: Late- but not early-onset blindness impairs audiohaptic multisensory integration

Chapter 3 Introduction

In chapter 2 we investigated the neural correlates of active touch using a size perception task in typically sighted children and adults. The findings supported previous suggestions of haptic dominance in childhood (Gori et al., 2008; Petrini et al., 2014). In this chapter, I will focus on the transition from sensory dominance to reliability-weighted (optimal) multisensory integration, and examine how the absence of vision, or a decrease in the quality of vision, affect this process.

While a number of studies have shown that optimal multisensory integration develops late in typically sighted individuals (usually after 8 years of age; Adams, 2016; Gori et al., 2008; Gori, Sandini, & Burr, 2012; Nardini et al., 2008; Petrini et al., 2014), it is still unknown whether visual loss or impairment before or after this time affects how this process develops. In fact, so far research in this field has focused on the effect of visual loss or impairment on the remaining single senses (Cappagli, Cocchi, & Gori, 2017; Collignon, Voss, Lassonde, & Lepore, 2009; Gori, Sandini, Martinoli, & Burr, 2014; Röder et al., 1999; Sathian & Stilla, 2010), returning contrasting results. That is, while some studies demonstrate a perceptual enhancement in the blind, other show an impairment of the remaining senses (see Kupers & Ptito, 2014 for a review). Furthermore, because compensation of vision loss does not necessarily need to arise from the reorganization of a single sense, but can also be achieved by combining the remaining senses in a more efficient way, knowing whether and how vision loss or impairment affects optimal integration of the remaining senses (e.g. sound and touch) is crucial to develop efficient rehabilitation treatments and aids.

In this study, using a similar task as in Chapter 2 and in Petrini et al. (2014), I assessed audiohaptic size discrimination performance in 92 sighted children and adults between 7-70 years, to provide a comprehensive overview of the developmental trajectory of optimal audio-haptic integration across the life span. Following from this, I tested how optimal audio-haptic integration develops in 29 children and adults with different levels of visual experience, focussing on individuals with low vision, and blind individuals that lost their sight at different ages during development.

By investigating the functional, behavioural benefit of audio-haptic integration in sighted and non-sighted individuals, this Chapter will provide a basis for the investigations of the neural correlates of audio-haptic integration presented in Chapter 4.

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Candidate's contribution to the paper (provide details, and also indicate as a percentage)	Meike Scheller made a considerable contribution to the conception as well as methodological design of the study (60%). The research process, including the acquisition of and analysis of data was conducted by Meike (95%). Meike also primarily executed the presentation of the study and associated data in journal format (90%), and presented associated content at national and international academic conferences.							
Statement from Candidate	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature.							
Signed	M.Scheller	Date	09.09.2019					

Late- but not early-onset blindness impairs audio-haptic multisensory integration

Meike Scheller¹, Michael J. Proulx¹, Michelle de Haan², Annegret Dahlmann-Noor^{3,4}, Karin Petrini¹

¹Department of Psychology, University of Bath; ²Developmental Neurosciences Programme, University College London, London, UK; ³ NIHR Biomedical Research Centre Moorfields; ⁴Paediatric Service, Moorfields Eye Hospital, London, UK.

Corresponding author: m.scheller@bath.ac.uk

Abstract

In order to accurately perceive and interact with the environment, sighted adults typically integrate information from different senses in an optimal fashion rather than using one sense at a time. Optimal integration allows to enhance perception by reducing sensory uncertainty. This is achieved through weighting sensory input based on the reliability of the different senses. However, optimal integration develops late in sighted children, usually not before eight years of age. Whether the development of multisensory integration in the intact senses is affected in visually impaired individuals is still unknown. Here we assessed the development of audio-haptic integration in sighted and visually impaired individuals across a large range of ages. First, we examined how audiohaptic integration develops and changes across the lifespan in 92 sighted (blindfolded) individuals between 7 to 70 years of age by using a child-friendly size discrimination task. We assessed whether audio-haptic performance resulted in a reduction of perceptual uncertainty compared to auditory-only and haptic-only performance as predicted by a maximum likelihood estimation model. We then tested how this ability develops in 28 children and adults with different levels of visual experience, focussing on low vision individuals, and blind individuals that lost their sight at different ages during development. Our results show that in sighted individuals, adult-like audio-haptic integration develops around 13-15 years of age, and remains stable until late adulthood. While early-blind individuals, even at the youngest ages, integrate audio-haptic information in an optimal fashion, late-blind individuals do not. Optimal integration in low vision individuals follows a similar developmental trajectory as that of sighted individuals. These findings demonstrate that visual experience is not necessary for optimal audio-haptic integration to emerge, but that consistency of sensory information across development is key for optimal multisensory integration to emerge.

Keywords: multisensory integration, development, plasticity, blindness, crossmodal

Research Highlights

- Adult-like audio-haptic integration develops at 13-15 years in sighted adolescents
- Optimal audio-haptic integration persists until late adulthood
- Early vision is not necessary for the development of optimal non-visual integration
- Late blindness impairs audio-haptic integration performance
- Sensory consistency is important for perceptual system development

Introduction

Early sensory input is crucial for the development of perceptual processes. A key method to discover the importance of early sensory input for perceptual development is to compare those who have had a sense, such as vision, impaired at an early developmental stage to those who acquire sensory deprivation later in life. For example, comparing humans who became blind early in life to those who became blind at older ages has revealed the impact of visual experience during development on other aspects of perception and cognition (Bedny et al., 2012; Pasqualotto, Furlan, Proulx, & Sereno, 2018; Wan et al., 2010a, see Scheller, Petrini, & Proulx, 2018 for a review). Reports on early-blind individuals with extraordinary auditory or tactile abilities have nurtured the idea that non-visual perceptual mechanisms improve in order to compensate for the lack of visual information (Goldreich & Kanics, 2003; Gougoux et al., 2004a; Kolarik, Cirstea, & Pardhan, 2013; Norman & Bartholomew, 2011; Röder et al., 1999; Vercillo, Milne, Gori, & Goodale, 2015; Voss et al., 2004). For example, it has been shown that the brain of the early blind allows for changes in perceptual function through cortical reorganisation (Amedi, Raz, Pianka, Malach, & Zohary, 2003; Collignon et al., 2015; Ortiz-Terán et al., 2016). Several neuroimaging studies to date revealed structural and functional changes in the blind brain, such as increased fine-tuning of the auditory cortex (Huber et al., 2019), the redeployment of the visual cortex for non-visual tasks such as auditory localization and Braille reading (Gougoux, Zatorre, Lassonde, Voss, & Lepore, 2005; Sadato et al., 1996), or enhanced functional connections between uni-sensory and multisensory processing areas (Ortiz-Terán et al., 2016). These changes, together with enhanced auditory and tactile sensory functioning (Amedi et al., 2003; Collignon et al., 2013), support the hypothesis of cross-modal compensation. That is, the brain adaptively compensates for lacking visual input early during development, leading to enhanced nonvisual perceptual functioning.

What several of these studies highlight is that the developmental timing of sensory deprivation determines how well an individual adapts to this perceptual state. That is, while congenitally-blind individuals show enhanced auditory pitch discrimination or horizontal localisation abilities, late-blind individuals do not exhibit such perceptual benefits (Gougoux et al., 2004b; Voss, Gougoux, Lassonde, Zatorre, & Lepore, 2006; Wan et al., 2010). Furthermore, studies on individuals that were born with dense bilateral

cataracts, and who received sight-restoring treatment within the first months of life, showed that even a brief, transient phase of visual deprivation early in life leads to longlasting changes in visual and non-visual information processing (Collignon et al., 2015; Geldart, Mondloch, Maurer, De Schonen, & Brent, 2002; Guerreiro, Putzar, & Röder, 2016; Putzar, Hötting, & Röder, 2010; see Maurer, 2017 for a review). This stresses that sensory experience plays a critical role particularly during early developmental periods, when heightened cross-modal plasticity allows the individual to learn about the physical principles of the environment and their relation to their own body through sensory-motor contingencies (de Klerk, Johnson, Heyes, & Southgate, 2015; Nagai & Asada, 2015).

The sighted adult brain can integrate multisensory information by weighting the different sensory inputs by their reliability, in order to reduce sensory noise and increase perceptual precision and accuracy (e.g. Ernst & Banks, 2002; Rohde, van Dam, & Ernst, 2016). For example, while one can often easily hold a conversation without directly looking at a conversation partner (e.g. over the phone), this task becomes much more difficult when standing at a busy street. Here, visual information of the partner's mouth movement can greatly enhance understanding of the conversation. However, the ability to optimally integrate sensory information has been found to only emerge late in childhood. While young children already possess the ability to make use of multisensory information (Neil, Chee-Ruiter, Scheier, Lewkowicz, & Shimojo, 2006), they do not perceptually benefit in the same way that adults do until 8-10 years of age (Adams, 2016; Gori, Sandini, & Burr, 2012), or even later (Nardini, Jones, Bedford, & Braddick, 2008; Petrini, Remark, Smith, & Nardini, 2014). For non-visual senses such as touch and sound, the developmental onset of optimal integration has not yet been established, but likely occurs after the age of 11 years (Petrini et al., 2014).

One prominent hypothesis, cross-modal calibration, accounts for this late development of optimal integration by suggesting that in early childhood the senses are kept separate to calibrate each other, thus impeding integration. During this time, the more robust sense for a certain task has been suggested to calibrate the less robust sense (Burr & Gori, 2012). For example, while touch is the more robust sense for estimating object size (Gori, Del Viva, Sandini, & Burr, 2008; Gori, Sandini, Martinoli, & Burr, 2010; Petrini et al., 2014), vision can be considered the more robust sense for estimating object orientation (Gori et al., 2008). In support of this hypothesis Gori and colleagues (2012) showed that haptic

orientation discrimination performance is impaired in blind children because vision could not calibrate touch on this task (Gori, Tinelli, Sandini, Cioni, & Burr, 2012). Indeed, several other studies demonstrated that perceptual functioning in the remaining senses of blind individuals is severely compromised (Cappagli, Cocchi, & Gori, 2017; Cappagli, Finocchietti, Baud-Bovy, Cocchi, & Gori, 2017; Vercillo, Burr, & Gori, 2016; Zwiers, Van Opstal, & Cruysberg, 2001) when accurate performance depends on high resolution visual input (Coluccia, Mammarella, & Cornoldi, 2009; Gori, Sandini, Martinoli, & Burr, 2014; Pasqualotto et al., 2018; Pasqualotto & Proulx, 2012; Vercillo et al., 2016).

Most of the aforementioned studies on cross-modal compensation and cross-modal calibration assessed how visual impairment influences perception in the remaining, single senses. For example, Cappagli, Cocchi and Gori (2017) showed that early-blind children and adults are severely compromised in the reproduction of hand pointing movements using proprioception, and struggle with extracting distance information from sound (Cappagli, Cocchi, et al., 2017). These findings show that unisensory processing in the remaining senses seems to depend on visual calibration early in development. However, much less is known about whether multisensory processes are affected by visual impairment in a similar way, although few studies tried to address this research question (Hötting and Röder, 2004; Champoux et al., 2011). It is still unknown how visual impairment affects optimal multisensory integration of the intact senses (e.g. audio-haptic optimal integration), and whether the onset and severity of visual impairment have a modulatory effect on it. As the visually impaired rely heavily on their remaining senses such as touch and hearing, it is crucial to understand when the ability to increase perceptual precision through optimal multisensory integration of the remaining senses is achieved. This knowledge would allow for the development of more effective sensory rehabilitation techniques that are functionally beneficial and meet the needs of the visually impaired individual (Ben Porquis et al., 2017; Gori, Cappagli, Tonelli, Baud-Bovy, & Finocchietti, 2016; Luo & da Cruz, 2016; Meijer, 1992, see Scheller, Petrini, & Proulx, 2018 for a review).

Here we used an optimised version of the audio-haptic size discrimination task from Petrini and colleagues (2014) to examine to what extent sighted and visually impaired adults and children reduce perceptual uncertainty by integrating sensory information from

touch and hearing. We chose an object size discrimination task as haptic information tends to be the most robust sense for it, even in sighted children (Gori et al., 2008; Petrini et al., 2014) and thus should allow for an unbiased comparison that is not driven by differences in task difficulty and familiarity between the different vision groups. Based on the cross-modal compensation hypothesis, whereby intact senses compensate for impaired ones, an increased use of the non-visual senses would predict an earlier developmental onset of audio-haptic integration in low vision and blind individuals compared to sighted individuals. Furthermore, due to increased developmental plasticity early in life (Cappagli, Cocchi, et al., 2017; Collignon et al., 2013) we would predict that congenitally- and early-blind adults benefit more from integrating audio-haptic information, compared to late-blind individuals. Based on the cross-modal calibration hypothesis, we would predict similar development of optimal audio-haptic integration in sighted, low vision, and blind individuals (independent of when vision was lost) as vision is not the most robust sense for this task and thus does not need to calibrate the other senses to achieve a more precise performance. Lastly, since recent findings (Cappagli, Finocchietti, Cocchi, et al., 2017; Cappagli, Finocchietti, Baud-Bovy, et al., 2017) have shown that children with low vision perform more similar to sighted than to blind children on different perceptual tasks, we predict that children and adults with low vision integrate audio-haptic information similar to sighted children and adults.

Methods

Participants

A total of 120 participants were recruited for this study. Of these, 46 were sighted adults (28 female, 41.6 ± 18.2 years of age) and 46 sighted children (32 female, 11.5 ± 2.5 years of age). They were grouped into five age groups in order to assess changes in multisensory integration over development. These age groups comprised of younger children (7-9 years), older children (10-12 years), adolescents (13-17 years), younger adults (18-44years), and older adults (45-70 years). For more details see Supplementary material S1. Furthermore, three adults (two female, 30 ± 16.8 years of age) and 11 children (six female, 10 ± 2.1 years of age) with low vision, as well as nine totally blind adults (three congenitally-blind, three early-blind, and three late-blind individuals, overall 3 female, 36 ± 19 years of age), and five totally blind children (all male, 12.6 ± 2.9 years of age)

participated in the experiment. This sample size is similar to other studies assessing perceptual functioning in children and blind individuals (Cappagli et al., 2017; Garcia et al., 2015; Gori et al., 2010, 2014). Details of visually impaired (VI) participants are depicted in Table 1 and 2. The difference of interest between these groups is the presence or absence of visual experience during and after the first eight years of life, as this has been suggested to be the age at which vision-driven cross-modal calibration ends and children start integrating multisensory information in an adult-like fashion (Burr & Gori, 2012; Cappagli et al., 2017).

All participants had normal hearing and no other certified developmental disorders, such as Autism Spectrum Disorder. Data from one blind child (VIc16) was excluded from the analysis due to inability to pay attention and complete the task due to hyperactive behaviour, leaving data of four blind children. Handedness was assessed using the Oldfield Edinburgh Handedness Inventory (Oldfield, 1971). All adults and parents of sighted and visually impaired children gave informed consent before participating in the study, which received ethical approval from the University of Bath Ethics Committee (ref # 15-211) and the National Health Research Authority (IRAS ref # 197917). Sighted adults and children were recruited through local schools, University advertisements, and Research Participation Panels. Visually impaired individuals were recruited through Moorfields Eye Hospital, Bristol Eye Hospital, local charities for the visually impaired, word of mouth, and University advertisements.

Participant	Sex	Age	Handedness	Age of Onset	Vision status	Diagnosis	Visual Acuity (Right Eye; Left Eye) [logMAR]	Vision group
Vla1	Female	18	Right	Birth	Congenitally Blind	Bilateral retinoblastoma, cataract, right enucliation	R - ; L = 2.8	СВ
Vla2	Male	59	Right	Birth	Congenitally Blind	Glaucoma	R > 3; L > 3	СВ
VIa3	Male	21	Right	Birth	Congenitally Blind	Congenital bilateral cataracts (until 9 years), Glaucoma, Retinal detachment		СВ
VIa4	Male	33	Right	5.5 years	Early Blind	Glaucoma	R > 3; L > 3	EB
VIa5	Female	18	Right	6 years	Early Blind	Retinitis pigmentosa	R > 1.8; L > 1.8	EB
VIa6	Female	19	Right	7 years	Early Blind	Stargardt disease	R = 2.8; L = 2.8	EB
Vla7	Male	60	Right	10 years	Blind	Leber's optic neuropathy	R = 1.5; L = 1.5	LB
la8	Male	61	Right	11 years	Blind	Stargardt disease	R = 2.8; L =2.8	LB
VIa9	Male	35	Right	25 years	Blind	Macular degeneration, Retinopathy	R > 3; L = 2.8	LB
VIa10	Female	49	Right	41 years	Low Vision	Pathological myopia, Choroidal neovascularization	R = 1.1; L = 0.8	LV
Vla11	Female	19	Right	Birth	Low Vision	Cataracts, Aniridia, Macular hypoplasia, Underdeveloped cornea	R = 1.1; L = 1.1	LV
Vla12	Male	21	Right	Birth	Low Vision	Ocular albinism, Nystagmus	R = 0.7; L = 0.7	LV

Table 1: Clinical and demographic information for blind and low vision adult participants.

Participant	Sex	Age	Handedness	Age of Onset	Vision status	Diagnosis	Visual Acuity (Right Eye; Left Eye) [logMAR]	Vision group
VIc1	Male	13	Right	Birth	Congenitally Blind	Bilateral microphthalmia, sclerocornea	R = 2.3; L = 2.3	СВ
VIc2	Male	12	Right	Birth	Congenitally Blind	Retinal dystrophy, Leber's congenital amaurosis	R > 3; L > 3	СВ
VIc3	Male	17	ambi./right	4 years	Early Blind	Retinal dystrophy	R > 3; L > 3	EB
VIc4	Male	9	Left	6 years	Early Blind	Glaucoma	R > 1.8; L > 3	EB
VIc5	Female	7	ambi./right	Birth	Low Vision	Oculocutaneous albinism, Hypermetropia	R = 0.88; L = 0.76	LV
VIc6	Male	11	Right	Birth	Low Vision	Red cone dystrophy	R = 0.7; L = 0.8	LV
VIc7	Male	12	Right	Birth	Low Vision	Bilateral juvenile retinoschisis	R = 0.76; L = 1.3	LV
VIc8	Female	13	Right	Birth	Low Vision	Stargardt disease	R= 1.0; L =1.0	LV
VIc9	Male	12	Right	Birth	Low Vision	Cone dystrophy	R = 0.58; L = 0.94	LV
VIc10	Male	9	Right	Birth	Low Vision	Stargardt disease	R = 1.0 ; L = 1.0	LV
VIc11	Female	7	Right	Birth	Low Vision	Stargardt disease	R = 1.0; L = 1.0	LV
VIc12	Female	11	Right	Birth	Low Vision	Stargardt disease	R = 1.04; L = 1.04	LV
VIc13	Male	11	Right	11 years	Low Vision	Neuromyelitis Optica	R = 1.5 L = 0.3	LV
VIc14	Female	9	Right	3.5 years	Low Vision	Bilateral optic atrophy, nystagmus	R = 1; L = 1.3	LV
VIc15	Female	8	Right	4 years	Low Vision	Stargardt disease	R = 0.4; L = 0.3	LV
VIc16*	Male	12	Right	Birth	Low Vision	Congenital Glaucoma, Left enculeation	R = 1.1; L = -	СВ

Table 2: Clinical and demographic information for blind and low vision child participants.

*data from this individual could not be used

Stimuli

Stimuli development was based on a standardised and validated method by Petrini et al. (2014). The stimuli consisted of 17 white, 3D-printed plastic balls of different sizes, ranging from 41mm to 57mm in diameter with an increment size of one millimetre. The median ball size with a diameter of 49mm was chosen as standard stimulus, leaving eight comparison stimuli bigger than the standard ball (50mm-57mm) and eight smaller comparison stimuli (41mm-48mm). A sound recorded from the standard ball with 49mm diameter was used to create the comparison balls sound. Praat software (Boersma, 2001) was used to modulate the sound in amplitude to match the sizes of all comparison balls, resulting in sixteen comparison sounds ranging from 71dB to 79dB. The increment size for auditory stimuli was 0.5dB and has been matched to the haptic stimuli in accordance with Petrini et al. (2014), in which 2mm haptic size increment were used with 1dB sound amplitude increments. Pilot tests confirmed the audio-haptic stimulus pair to be well adjusted.

Procedure

The participant was seated comfortably in a chair in front of a table and was blindfolded in order to eliminate any visual cues during the experiment. The set up on the table comprised of a touch screen panel on which the haptic stimuli (plastic balls) were placed during the experiment, one at a time (see Fig. 1Figure 1:). A thin layer of foam between the ball and touch screen prevented the stimuli from generating impact sounds when being placed down. The set up was covered with a black cloth before the experiment and during breaks so that participants remained naïve about the set up and did not gain visual information about the stimulus range. The participant's dominant hand rested on a soft foam block, which was positioned next to the touch screen. During each trial, a ball was placed on the touch screen in front of the participant, who was then asked to briefly tap the ball with the straight and flat palm of their dominant hand. As the participant was blindfolded, their hand was guided by the experimenter. Once pressure was sensed on the touch screen the corresponding sound, which provided the auditory size information, was played back through headphones. After tapping the ball, the hand was returned to the soft foam block and the same procedure was repeated with a second stimulus. After two stimuli (unimodal) or two stimuli-pairs (bimodal) were presented, the participant was asked to indicate whether the first or the second object was bigger. Before each experimental block (condition), participants received training on at least four practice trials in order to indicate whether they were able to do the task and to familiarize them with the stimuli.



Figure 1: Experimental set up and procedure. All participants were blindfolded and sat in front of the set up with their dominant hand resting on a semi-soft foam surface. (1) Haptic stimuli were positioned in a pre-defined location on a thin foam surface that was placed on a touchscreen in front of the participant. (2) Their dominant hand was guided to the location of the stimulus, which they briefly tapped with the flat and straight hand. In the haptic condition, only information from touch was available. In the bimodal conditions, the pressure that was sensed by the touch screen elicited the size-corresponding sound to be played back through headphones. In the audio only condition, participants held a pen, which they used to tap on the touch screen to trigger the sound. In this condition their hand was guided as well. (3,4) The same procedure repeated for a second stimulus. Participants were then asked to judge which of the two objects was bigger.

During each trial, the standard stimulus (49mm ball, 75dB sound) was compared to either a bigger or a smaller stimulus. The order in which standard or comparison stimuli were presented was randomized – with the standard being either first or second. The following stimulus conditions were grouped into blocks of 30 trials in a counter-balanced order: (a) audio only, (b) haptic only, (c) bimodal congruent, and (d) bimodal incongruent. In the audio-only condition, participants only discriminated between object sizes based on the sounds they heard through headphones. Sounds were triggered by participants tapping on the touch screen with a pen. Their hand was guided by the experimenter in order to match the timing of arm movement in the other blocks. Triggering the sound through tapping was used to allow comparison between blocks that all used active arm movement and to control for attentional shift due to expected sound onset. In the haptic only condition, participants tapped the ball, but the sound was not played back. Bimodal congruent presentations played the corresponding sound when the ball was tapped. In the bimodal incongruent condition sound and touch gave conflicting size information. i.e. a bigger ball (53mm) was presented with the sound of a smaller ball (73dB = 45mm), together averaging on the standard stimulus size (49mm). This cross-modal conflict between haptic and auditory information can be used to determine the degree of perceptual bias towards one of the two cues, and with that the relative reliability (or attributed weight) of the two modalities for this task. We used only one incongruent condition, as Petrini et al. (2014) reported no differences between incongruent pairings. Limiting the length of the experiment is especially important with respect to testing children and individuals with shorter attention spans. Responses were used to calculate discrimination thresholds for each condition, which serve as a measure for perceptual precision. Lower discrimination thresholds indicate a higher perceptual precision. For further information on the procedure and data analysis, see the Supplementary material S2.

Results

Size discrimination thresholds were used as a measure of precision and were estimated for all participants and conditions separately. All data were assessed for normality, homogeneity of variances and outliers before appropriate tests were chosen. Test assumption checks are reported in the Supplementary material S3.

To assess how size discrimination thresholds for audio, haptic, and audio-haptic stimuli differ between age groups we carried out a mixed factorial ANOVA, using the three conditions as within-subjects factor and age group as between-subjects factor. The analysis indicated significant main effects for age (F(4,87) = 8.975, p < .001) and condition (F(2,174) = 12.93, p < .001), as well as a significant interaction between age group and condition (F(8,174) = 2.856, p = .005). Bonferroni-corrected, paired t-test were used to compare discrimination thresholds between age groups. Below, we report corrected p-values. Effect sizes were computed as Hedges *g* with correction for small sample sizes ($d_{unbiased}$, Cumming, 2012). Younger adults performed significantly better in the audio-haptic bimodal condition than with either auditory (t(29)=4.85, p < .001, $d_{unb} = 0.874$) or haptic (t(29) = 2.28, p = 0.015, $d_{unb} = 0.411$) information alone. Similarly, the older adults performed significantly better in the bimodal condition than in either the auditory (t(14)=4.06, p = .002, $d_{unb} = 1.018$) or haptic (t(14)=4.10, p = .002, $d_{unb} = 0.703$) condition. In both the young and older children groups, thresholds in the bimodal

condition were not smaller than in either the auditory-only (7-9yo: t(7) = 0.239, p = 1, $d_{unb} = 0.153$; 10-12yo: t(21) = 1.15, p = .394, $d_{unb} = 0.241$) nor haptic-only (7-9yo: t(7) = 0.241) 0.45, p = 1, $d_{unb} = 0.203$; 10-12yo: t(21) = 2.32, p = 1, $d_{unb} = 0.485$) condition. In adolescents, bimodal discrimination thresholds were significantly lower than in the auditory-only condition (t(14) = 3.01, p = .014, $d_{unb} = 0.756$), but only marginally lower than in the haptic-only condition (t(14) = 2.32, p = .054, $d_{unb} = 0.584$) condition. The results are depicted in Fig. 2, showing a clear trajectory of the improvement of size discrimination performance with age. In order to compare discrimination performance in the multisensory condition with Bayes-optimal integration performance, we calculated predictions for discrimination thresholds based on maximum likelihood estimation (MLE, see equation 1.3 and 1.4 in Supplementary material S2) for each individual separately. Averages for predicted bimodal thresholds are depicted in Fig. 2 as black circles. For more details on individual integration performance see Supplementary material S4. Comparing the bimodal threshold to MLE prediction, we found that only in the two adult groups discrimination thresholds did not differ from MLE prediction (18-44 year-olds: $t(29) = 2.1, p = .133, d_{unb} = 0.379; 45-70$ year-olds: $t(14) = 0.94, p = 1, d_{unb} = 0.229$. Sensory weights for auditory and haptic cues indicated that all groups, apart from older adults, weighted haptic cues stronger than auditory cues. For more details on cue weighting see Supplementary material S5.



Figure 2: Unimodal and bimodal discrimination thresholds of sighted individuals of different ages. Average size discrimination thresholds for all conditions across five age groups. Measured discrimination thresholds for auditory-only (blue triangles), haptic-only (red squares), as well as bimodal (green circles) conditions plotted for five age groups, including younger children, older children, adolescents, as well as younger and older adults. Black circles represent the average discrimination thresholds predicted by Bayes optimal prediction (MLE) and were calculated as a weighted combination of the two unimodal estimates for each individual. Error bars represent 95% CIs.

To examine the extent to which the development of audio-haptic integration depends on visual input, we assessed audio-haptic discrimination performance in adults and children with different levels of visual experience. Thereby we focused on individuals with reduced visual input (low vision, logMAR < 1.3, n = 15) and no functional visual input (blind, logMAR ≥ 1.3 ; n = 14) separately. The grouping was based on the WHO definition of blindness using individual visual acuity measures (World Health Organization, 2018). In the low vision group, integration performance was compared between adults and children to assess whether a reduction in visual input affects how audio-haptic integration develops. To assess how the absence of vision and the developmental timing of vision loss affect audio-haptic integration, we then compared integration performance between blind adults with three different onsets of vision loss: congenitally blind, early blind, and

late blind. We chose eight years as a developmental cut-off age to differentiate between early and late blind, as this has been identified as the earliest age at which adult-like multisensory integration emerges in sighted children when using vision (Adams, 2016; Gori et al., 2008; Nardini et al., 2008, see Fig. 8 in discussion). Furthermore, it has been proposed that vision-driven cross-modal calibration takes place within the first eight years of life (Cappagli et al., 2017). In cases where both eyes were affected differently (e.g. participant VIc13) the visual function of the better eye was used as an approximation of best visual function. Non-parametric tests were applied for all analyses including visually impaired individuals as the sample size was small in all sub-groups. Bonferroni-corrected Mann-Whitney U tests were used for group comparisons, while Crawford-Howell casecontrol comparisons (Crawford, Garthwaite, & Porter, 2010) were used for individual performance comparisons.

The influence of reduced visual input on audio-haptic integration was examined by comparing discrimination thresholds of children and adults with low vision against the respective developmental group of sighted participants. Comparing low vision children (aged 7-12 years) with sighted children (aged 7-12 years) showed that discrimination thresholds did not significantly differ between groups in neither auditory-only (U = 151, p = 1, r = 0.04), haptic-only (U = 158, p = 1, r = 0.10), nor audio-haptic (U = 171, p = 1, r < 0.01) conditions. Furthermore, there was no difference between adults with low vision and adults with typical sight in either condition (auditory: U = 74, p = 1, r = 0.04; haptic: U = 39, p = .674, r = 0.18; audio-haptic: U = 43, p = .890, r = 0.15, see Fig. 3).



Figure 3: Unimodal and bimodal discrimination thresholds of sighted and low vision individuals. Average size discrimination thresholds of both unimodal and bimodal conditions, as well as Bayes optimal prediction (MLE). Left panel shows average thresholds for children, while the right shows discrimination panel thresholds for adults, with the sighted group averages plotted as reference. Error bars represent 95% CIs.

The influence of functional visual input on audio-haptic integration was assessed by comparing discrimination thresholds of typically sighted children and adults to that of blind children and adults with different onsets of blindness (congenitally, early, and late blind). Each individual blind child was compared to the respective age group described in the sighted section above (7-9years, 10-12years, 13-17 years) using Crawford-Howell t-tests for case-control comparisons. Most comparisons did not reach significance (p > .05), however, the 9-year old early-blind child showed a significantly lower discrimination threshold only in the bimodal condition, compared to sighted 7-9 year olds (t = 3.47, p = .025, zCC = 3.66, see Fig. 4).

Discrimination thresholds of blind adults were assessed, similar to low vision adults, on the basis of group comparisons using Bonferroni-corrected Mann-Whitney U-tests. There were no significant differences between the congenitally-blind, nor the early-blind individuals and sighted adults in either the auditory (CB: U = 47, p = 1; EB: U = 83, p =1), haptic (CB: U = 35, p = .499; EB: U = 67, p = 1), or audio-haptic conditions (CB: U= 91, p = .951; EB: U = 82, p = 1). However, the late-blind individuals differed from sighted adults in the audio-haptic condition, showing higher discrimination thresholds (U= 9, p = .038, r = 0.36, see Fig. 4), while they did not differ in either auditory (U = 108, p = .254) or haptic thresholds (U = 91, p = .951).



Figure 4: Discrimination thresholds for unimodal and bimodal performance for sighted and blind individuals. Average size discrimination thresholds for both unimodal and bimodal conditions, as well as Bayesian model prediction (MLE). Panel A shows thresholds for two blind children aged 9 and 12, as well as the average thresholds for children aged 7-12 years. Panel B shows thresholds for two blind adolescents aged 13 and 17, together with the average thresholds for 13-17-year-old sighted adolescents. Panel C shows average thresholds for reference on the left. Early blindness is defined as having an onset within the first 8 years of life, while late blindness is defined by an onset after 8 years of life, in line with the duration of cross-modal calibration (Burr & Gori, 2012). Black circles represent the average discrimination thresholds predicted by maximum likelihood estimation based on a weighted combination of the two unimodal estimates. Error bars represent 95% CIs.

Multisensory benefit ($\Delta_{\text{measured-predicted}}$)

We next computed the differences between bimodal discrimination thresholds and MLE predictions $\Delta_{\text{measured-predicted}}$ for each individual. This measure provides a quantified estimation of the perceptual benefit that is gained through multisensory integration. Differences between bimodal threshold and MLE prediction across the developmental age range are depicted for sighted individuals in Fig. 5, and for low vision and blind individuals in Fig. 7.

Comparing the multisensory benefit $\Delta_{\text{measured-predicted}}$ of young adults with the different developmental age groups, we found young adults and older adults did not differ from each other (t(29) = 0.33, p = 1 $d_{unb} = 0.101$). Furthermore, the multisensory benefit of adolescents aged 13-17 years did not differ from that of young adults either (t(35) = 1.23, p = .568, $d_{unb} = 0.357$). Contrastingly, older children as well as young children

significantly differed from young adults in the perceptual benefit gained through multisensory integration (7-9yo: t(9) = 2.81, p = .039, $d_{unb} = 1.319$; 10-12 yo: t(35) = 4.19, p < .001, $d_{unb} = 1.231$; see Fig. 5).



Figure 5: Integration performance of typically sighted individuals. Left panel shows individual threshold differences between predicted and measured discrimination thresholds for audio-haptic bimodal stimulus presentation across all ages. The dashed line at y = 0 indicates optimal performance predicted by MLE, which is based on the auditory and haptic unisensory estimates. Data below this line indicates an increase in precision that is better than predicted by the model. Different colors correspond to the different age groups: young children (7-9 years), older children (10-12 years), adolescents (13-17 years), younger adults (18-44 years), and older adults (45-70 years). Light grey trend line indicates the line of best fit. The right panel shows means for discrimination threshold difference scores (Δ) for each age group separately. Error bars indicate 95% CI. * = p<.05; ** = p< 0.01; n.s. = not significant.

In order to assess how integration performance develops in low vision individuals we compared the multisensory benefit $\Delta_{\text{measured-predicted}}$ between sighted and low vision children, and between sighted and low vision adults. Average scores were not significantly different between sighted and low vision individuals, this was true for both children (U = 158, p = .735, r = 0.10) and adults (U = 83, p = .543, r = 0.02, see Fig. 6).



Figure 6: Integration performance of low vision and blind individuals. Differences between predicted and measured discrimination thresholds for bimodal stimulus presentation. A panels show average multisensory benefit scores for children, and individual multisensory benefit scores for adults with low vision (light circles). The average multisensory benefit scores of the respective, age-matched sighted groups are plotted as references. B panels show multisensory benefit for individual congenitally-blind (black), early-blind (grey), and late-blind (light grey) individuals. Early and late blindness are defined by the onset of blindness either before or after the age of 8 years. For the children and adolescents, individual ages and age ranges are indicated next to the data points to allow for a direct comparison. The dashed line at y = 0 indicates MLE model prediction based on the auditory and haptic unisensory estimates, while data below this line indicates an increase in precision that is better than predicted by the model. Error bars indicate 95% CI.

Comparing the average $\Delta_{\text{measured-predicted}}$ between individual blind children and the agematched sighted children (7-12years) or adolescent (13-17years) groups indicated that the congenitally-blind 9-year old benefitted from integrating audio-haptic information significantly more than sighted children (t = 1.92, p = .032, zCC = 1.96). For the 12-year old early-blind individual, there was a marginal difference (t = 1.69, p = .051, zCC = 1.72, suggesting that this individual also reduced uncertainty more than sighted children. We did not find any differences between the 17-year old congenitally-blind individual and sighted adolescents (t = 0.25, p = .105, zCC = 1.36), nor for the 13-year-old early-blind individual and sighted adolescents (t = 0.25, p = .403, zCC = 0.26). Next, we compared sighted adults with blind adults in three different blindness onset groups (congenitally, early, late blind). Congenitally-blind individuals integrated audio-haptic information optimally, or even supra-optimally (see Fig. 6). This group differed from sighted adults only marginally (U = 112, p = .059, r = 0.24). Discrimination thresholds of early-blind individuals did not differ significantly from that of sighted adults (U = 92, p = .322, r = 0.07). Lastly, late-blind individuals showed significantly higher $\Delta_{\text{measured-predicted}}$ scores compared to sighted individuals (U = 5, p = .002, r = 0.448), indicating reduced integration performance. Fig. 4 shows late-blind adults exhibit similar auditory and haptic thresholds as other adults. Differences between bimodal threshold and MLE prediction for blind children and adults, as well as the respective sighted age groups, are depicted in Fig. 6. For an overview of individual scores for adults and children from all vision groups across the developmental age range see Fig. 7.

Due to differences in sample characteristics, such as a higher proportion of males in the visually impaired groupcompared to sighted children and adults, group differences were further assessed between the visually impaired and age- and sex-matched subsamples of sighted participants (adults). Mann-Whitney U-tests confirmed the findings reported above, indicating only late-blind (U = 1, p = .008), but not congenitally-blind (U = 51, p = .088) or early-blind (U = 42, p = .359) adults, as well as adults with low vision (U = 19, p = .275) significantly differed from their sighted counterparts. Furthermore, children (aged 7-12 years) with low vision did not significantly differ from their age- and sexmatched sighted control group either (U = 61, p = .371) or the blind 12 year old (t = 1.54, p = .074). However, the blind 9 years-old showed significantly stronger multisensory benefit than the control group of sighted males (t = 1.82, p = .045). Individual measures as well as group measures of multisensory benefit for visually impaired individuals are shown in Fig. 7.



Figure 7: Overview of multisensory integration performance in low vision and blind individuals: Panel A shows individual difference scores for measured versus predicted discrimination thresholds as a function of age. Predicted threshold, indicated by the grey dashed line at y = 0, is based on the Bayesian integration model predicting optimal integration performance. Model predictions have been calculated for each participant separately and are based on the individual auditory and haptic unisensory thresholds. Individuals are color-coded based on different amounts of visual experience. Panel B shows average scores for low vision and blind children and adolescents, with an age-matched sample of sighted children and adolescents plotted as a reference. Panel C shows average scores for low vision and blind adults, depending on the age of blindness onset. Average scores for a matched sample of sighted adults are plotted as a reference. Error bars indicate 95% CI.

Discussion

The brain's ability to enhance perceptual precision by integrating input from multiple senses develops late in sighted individuals (Adams, 2016; Gori et al., 2008; Nardini et al., 2008; Petrini et al., 2014). Early blindness has been shown to impact on non-visual perception in two ways: on the one hand, neural plasticity allows the individual to cross-modally compensate for missing sensory input, for example through enhanced tactile discrimination or auditory localisation (Amedi et al., 2003; Collignon et al., 2013). On the other hand, blindness precludes the calibration of the non-visual senses through vision. This has been shown to lead to impaired auditory or proprioceptive spatial perception (Cappagli et al., 2017; Gori et al., 2014). However, as most of our environment is multisensory, and as visually impaired individuals rely more heavily on other senses such as touch and hearing, the functional outcomes of visual deprivation on the benefits of audio-haptic integration (reducing sensory uncertainty by combining sensory information) are of fundamental importance.

Here we report, for the first time, that while congenitally- and early-blind (EB) adults show similar or even marginally better integration performance than sighted adults, audio-haptic integration performance of late-blind adults appears impaired. As expected, the developmental period during which visual experience influences the development of audio-haptic integration extends until eight to nine years of life. This falls in line with the previously proposed period of cross-modal calibration through vision (Cappagli et al., 2017; Gori et al., 2014). Based on the idea that during development the more robust sense calibrates the less robust senses, we would expect that the presence or absence of visual experience would not affect the performance on our audio-haptic size discrimination task. This is because touch is the more robust sense for assessing size information, compared to audition (Petrini et al., 2014; present study) or vision (Gori et al., 2008, 2012). Indeed, we find that blindness early in life does not affect audio-haptic integration later in life, which would therefore support the idea that the more robust sense teaches the less robust sense and that vision is not necessary for audio-haptic integration. However, we also find that early blindness seems to lead to an earlier development of optimal audio-haptic integration. This finding would support the idea of cross-modal compensation. That is, an increased use of the remaining senses leads to an enhanced recruitment of presumptive "visual" areas in the brain to process non-visual information, thereby enhancing performance in those senses (Amedi et al., 2003; Collignon et al., 2013). However, in contrast to both these theories our data suggests that late blindness, which indicates the presence of visual experience during early development, leads to a disruption in audio-haptic integration performance. Interestingly, while the presence of visual experience early in life seems to reduce audio-haptic integration performance in the late blind, it does not reduce integration performance in the sighted. These findings cannot be explained by either cross-modal calibration or sensory compensation alone.

Previous studies that reported perceptual differences between individuals with different levels of visual experience showed that congenitally-blind individuals performed significantly worse than sighted individuals on different auditory and proprioceptive spatial perception tasks. At the same time, late-blind and low vision individuals performed similar or even better than sighted individuals (Cappagli, Cocchi, et al., 2017; Cappagli, Finocchietti, Baud-Bovy, et al., 2017). These findings suggest that the mere presence or absence of visual input early in life affects spatial processing in the remaining senses. Interestingly, the effect of visual deprivation shows the opposite pattern in our study. A possible explanation for this opposing trend is that the present study is targeting different processes. While Cappagli et al. (2017) used a task for which vision was the most robust sense and examined the effect of visual experience on proprioception and audition separately, our study used a task for which touch was the most robust sense and we examined the effect of visual experience on the integration of touch and audition. Therefore, if vision was the most robust sense for a task, only early, but not late blindness, would affect non-visual processing later in life (Cappagli, Cocchi, et al., 2017). If touch, on the other hand, is the more robust sense for a task, early blindness should not affect non-visual processing later in life. Late blindness could, however, still affect non-visual processing if the perceptual process (e.g. non-visual multisensory integration) is dependent on the developmental consistency of sensory experience. Our results and previous findings therefore support both cross-modal compensation and cross-modal calibration. However, the results also suggest that these processes serve an adaptive purpose by allowing early sensory experience to imprint on the developing brain and preparing the developing individual for the sensory environment they are likely to experience later in life. That is, throughout the first eight years in life, the system accumulates sensory experience in order to gauge the reliability of the different sensory modalities that they will likely use later (Noppeney, Ostwald, & Werner, 2010), and to
distribute modality-specific weights accordingly (Rohe, Ehlis, & Noppeney, 2019). If the early sensory environment (e.g. typical sight) does not match up with the environment that the individual experiences later in life (e.g. blindness), the system might attribute higher weights to the wrong (i.e. impaired) sensory modality. At this point, it is worth noting that while the present data provides first evidence for late-onset blindness impairing the development of optimal audio-haptic integration, it is based on a small sample of three adult individuals. Future studies need to corroborate this finding with a larger sample of late-blind individuals by drawing on the distinction of early-onset and late-onset blindness (before/after 8-9 years) presented here and in Cappagli et al. (2017).

The second aim of this study was to provide a comprehensive trajectory of the development of audio-haptic integration across the life span in sighted humans. To the best of our knowledge, only one study (Petrini et al., 2014) so far assessed how optimal audio-haptic integration develops between middle childhood (5-11 years) and young adulthood (19-35 years). They found that audio-haptic multisensory integration is not yet fully developed by the age of 11 years, with the onset of this integration remaining unknown. Our results replicate these findings, but also show that audio-haptic integration becomes more adult-like at around 13-15 years in typically sighted individuals. This is evidenced by a similar weighting of sensory cues, and a reduction in sensory uncertainty between adolescents and young adults. Arguably, the maturation of this process is still ongoing for several individuals at this age, while the majority of adolescent participants in our study benefitted from having both sensory cues available. This likely explains why the adolescent group showed a reduction of uncertainty in the audio-haptic condition compared to auditory-only or haptic-only conditions, but still differed in measured and predicted discrimination thresholds (for individual data and discussion see Supplementary material S4 and S4.2) (Jonas, Spiller, Hibbard, & Proulx, 2017; Murray, Thelen, Ionta, & Wallace, 2018; Peterzell, 2016). Finally we found that, overall, the haptic information dominated object size perception, confirming the haptic dominance for this task over other senses, which is in line with the findings of previous developmental studies (Gori et al., 2008, 2010; Petrini et al., 2014).



Figure 8: Developmental onset of adult-like multisensory integration: Reported age of onset of adult-like multisensory integration for different sensory systems. Colour combinations indicate the sensory combinations that have been tested by respective studies and tasks. All identified ages of onset fall within a period of 8-14 years, coinciding with major developments in fronto-parietal networks (Giedd et al., 1999; Gogtay et al., 2004) governing multisensory weighting (Cao et al., 2019; Rohe et al., 2019). Black boxes at the right end of the developmental trajectory indicate that multisensory integration performance has not yet reached adult-like levels at this age, but is likely to develop later (indicating the upper boundary of the age range tested in each respective study). Note that several studies did not report a concrete age of onset, but an age range during which this ability develops. The figure presents mean age of these age ranges.

The summary shown in Fig. 8 suggests that the onset of adult-like integration and possibly the end of cross-modal calibration (Burr & Gori, 2012) may differ for the different senses and tasks (see also Fig. 3 in Stanley, Chen, Lewis, Maurer, & Shore, 2019). For example, the perception of temporal properties (Adams, 2016; Gori, et al., 2012) proceeds the integration of spatial characteristics (Gori et al., 2012). This is also in line with a number of studies showing that audio-visual, visuo-tactile, and audio-tactile simultaneity perception develops adult-like characteristics before the respective spatial information is integrated (Chen, Lewis, Shore, Spence, & Maurer, 2018; Chen, Shore, Lewis, & Maurer, 2016; Stanley, Chen, Lewis, Maurer, & Shore, 2019), suggesting that temporal simultaneity perception is a prequisite for the integration of spatial information. However, the onset of optimal multisensory integration also seems to depend on the sensory modality pairing that is involved in the task. For example, while audio-visual optimal integration seems to develop between 8-12 years of age (Adams, 2016; Gori et al., 2008;

Gori, Sandini, et al., 2012; Nardini, Bedford, & Mareschal, 2010; Petrini et al., 2016), the integration of non-visual information does not emerge until later (Petrini et al., 2014; *present study*).

The consistent late maturation of optimal integration shown by several studies (Fig. 8) could be a consequence of the late maturation of the substrates that subserve optimal multisensory integration. While early sensory processing areas mature relatively early in childhood, frontal and parietal regions have been shown to develop last, with maturational peaks around late childhood and adolescence (Giedd et al., 1999; Gogtay et al., 2004; Sowell et al., 2003). Notably, there has been long-standing evidence of the modulatory involvement of a fronto-parietal network in the optimal integration of multisensory information (Engel, Senkowski, & Schneider, 2012; Jones & Powell, 1970; Ma, Beck, Latham, & Pouget, 2006). However, specific evidence for the neural basis of multisensory reliability weighting in frontal (Cao, Summerfield, Park, Giordano, & Kayser, 2019) and parietal (Boyle, Kayser, & Kayser, 2017; Rohe et al., 2019) areas has only been provided recently. Taken together with the findings summarized in Fig. 8, this might suggest that the functional onset of optimal multisensory integration depends on the maturation of these networks, leading to a sensory-specific onset in late childhood and early adolescence. Evidence for a link between optimal cue integration within one modality and maturational changes in their processing substrate has previously been provided by Dekker and colleagues (2015).

Conclusion

Our results show that the ability to combine audio-haptic sensory input in an optimal way does not develop before adolescence (13-17 years) in typically-developing, sighted individuals. The data further provide empirical evidence that visual experience is not necessary for non-visual optimal multisensory integration to emerge, but that consistency of sensory experience plays an important role in setting up the rules under which information is integrated later in life. They highlight that the adaptiveness of cross-modal plasticity lies in preparing the developing individual for the sensory environment they are likely to experience later in life. That is, during development, the system accumulates sensory experience in order to gauge the reliability of the different sensory modalities,

and to distribute modality-specific weights accordingly. If the early sensory experience (e.g. sighted) does not match up with what the individual experiences later in life (e.g. blindness), the system might attribute higher weights to the wrong (lost or impaired) sensory modality. Our results further suggest that the calibration of the perceptual weighting system is taking place during approximately the first eight to nine years of life, highlighting the important role of early multisensory experience during this developmental period.

Chapter 3 – Conclusion

In this study, we assessed how optimal audio-haptic integration develops over the life span in sighted individuals, and how it is influenced by visual experience. I have shown that optimal integration of sound and touch information develops in adolescence, starting around the age of 13 years and increasing until adulthood. Furthermore, by using the same task in a group of older adults, I showed that the ability to integrate audio-haptic information optimally stays stable over the course of adult development. This study further found that visual experience during development influenced audio-haptic integration, however, only some of these findings could be explained by current theories. Based on the hypothesis that sensory compensation in blindness allows for a more efficient processing of non-visual sensory information, we would have expected an earlier onset of multisensory integration in visually impaired individuals. Indeed, we showed that totally blind children showed optimal integration performance before the age of 13 years. Children with some residual vision on the other hand, showed a similar development as sighted children. This suggests that non-visual multisensory integration is rather influenced by the presence rather than the quality of visual input.

To this end, we do not know whether this effect is due to the absence of visual input per se, or to an increased use of the non-visual senses. A more efficient calibration through the dominant sense, active touch, might facilitate this early development in blind children. In fact, the idea that sensory experiences accumulate over time in order to influence perceptual weighting (Noppeney, Ostwald, & Werner, 2010; Turner, Gao, Koenig, Palfy, & McClelland, 2017) would support the idea of an experience-dependent re-weighting. However, the present data does not offer us to draw definite conclusions about this, and future research would be needed to assess whether this compensation might be due to a long-term accumulation of sensory experience.

One finding that could not be explained based on currently existing theories is the impairment of optimal audio-haptic integration in late-blind individuals. Given the current theories on cross-modal calibration and sensory compensation, this finding might seem somewhat counter-intuitive. As late-blind adults and sighted adults shared similar visual experience during the first 8-9 years of life, this effect cannot be explained by either cross-modal calibration or sensory compensation before this age. Therefore, the impairment in optimal multisensory integration of the remaining senses in late-blind adults must be a result of changes in sensory processing after the age of 8-9 years. What

those groups that share the ability to reduce sensory uncertainty through multisensory integration (sighted, low vision, congenitally- and early-blind individuals) have in common is the consistency of sensory environment across development. That is, the presence (or absence) of vision in late childhood, around the age of 8-9, years influenced the later development of audio-haptic integration. In fact, the late blind did not only combine information in a sub-optimal way, they performed worse with both senses compared to one sense alone. This might suggest that adding a second sense distracts individuals rather than facilitating multisensory integration.

Another interesting finding is that the majority of our congenitally-blind participants integrated auditory and haptic information in an almost supra-optimal fashion. That is, integration of multisensory information allowed them to reduce uncertainty to an extent that was better than predicted by the MLE model. While supra-optimal performance was also present in individual sighted adults, it seemed to be more enhanced in congenitally-and early-blind individuals. Given that 'optimality' is approximated based on the sensory reliability of the two single senses, such supra-optimal performance is surprising and potential reasons for this should be discussed.

During the size discrimination task, participants were presented with either one or two stimuli at the same time. Therefore, the amount and reliability of information could not exceed that of the information delivered during a trial. However, prior knowledge or increasing familiarity with the stimuli could be used to gain additional information about the objects. That is, given that the same standard stimulus was used in each trial (except in the incongruent condition) supra-optimal integration of multisensory cues can result from perceptual learning of the stimuli over the course of several trials (Rohde et al., 2016). In order to prevent stimulus-learning throughout the task, participants received no feedback during the blocks. However, a design whereby experimental conditions are split into separate blocks and trials within the same condition are repeated, might increase the chances for participants to become more familiar with the stimuli. This learnt information would facilitate discrimination between the standard and comparison stimuli. Given that the same paradigm was applied in all groups, this might indicate that congenitally-blind individuals are more efficient in creating internal representations based on haptic and auditory information that might then be used as a perceptual prior affecting the integration of sensory estimates.

However, it is also likely that supra-optimal integration performance results from a violation of the assumptions made by the Bayesian optimal observer model. That is, the model assumes noise in both sensory processing streams to be independent (Rohde et al., 2016). In other words, if auditory and haptic neural processing takes place independently of each other, supra-optimality is statistically impossible. However, synergy between the cortical processing pathways would violate this assumption. Thereby, processing in one sensory modality might inhibit noise processing in the other modality, thereby 'funnelling' the perceptual representation (Collignon et al., 2013). In fact, while crossmodal cortico-cortical connections are known to exist in the sighted (Klinge, Eippert, Röder, & Büchel, 2010), and to cross-modally influence sensory processing (Ricciardi, Bonino, Pellegrini, & Pietrini, 2014; Schroeder & Foxe, 2005), they have been found to be enhanced in the blind (Bavalier & Neville, 2002; Klinge et al., 2010; Collignon et al., 2013; Wittenberg, Werhahn, Wassermann, Herscovitch, & Cohen, 2004), likely due to early neural reorganisation. A recent study on rats that showed robust supra-linear integration performance (Nikbakht et al., 2018; see Shalom & Zaidel, 2018 for a commentary) strongly suggest that the processing pathways of simultaneously received visual and tactile inputs might in fact not be independent. This may account for supraoptimal performance.

In order to examine the neural correlates that determine the behavioural differences in optimal multisensory integration between sighted and non-sighted individuals, the same participants were invited to take part in a second study that investigated the neural basis of audio-haptic integration by using electrophysiological recordings. This study will be described and discussed in Chapter 4.

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Chapter 4: Neural correlates of audio-haptic integration in sighted and non-sighted individuals

Chapter 4 Introduction

As shown in Chapter 3, we found that the integration of audio-haptic information follows the rules of the Bayesian Optimal Observer model in typically sighted adults, as well as congenitally- and early-blind adults. While this integration was approaching optimality in typically sighted adolescents, those individuals that lost their sight after the age of 8 years showed an impaired ability to integrate the remaining senses efficiently. In this Chapter, I investigate the underlying neural processes that may give rise to these behavioural differences. This study employs an Event-Related-Potential (ERP) paradigm, combined with an adaptation of the previously used audio-haptic size discrimination task. As ERPs require a frequent repetition of stimulus presentation, and the recording duration is limited both by participant attention span and a decrease of signal to noise ratio throughout the task, the number of stimulus sizes used was reduced to two. This allowed me to increase the frequency with which each stimulus was presented in all of the different conditions. Furthermore, as congenitally and early blind adults integrated audio-haptic information in a similar way, these individuals were combined into one group.

Chapter 2 showed that ERPs could reliably be measured despite extensive arm movements when using active touch. However, due to the variation in movement information between the conditions used in Chapter 2 we were unable to compare these directly. In the current study, evoked potentials of the multisensory (audio-haptic) conditions were directly compared to the sum of the evoked responses of the unisensory (auditory and haptic) conditions while keeping the movement information consistent between conditions. A deviation of the multisensory evoked potential (composed of the two sensory signals occurring simultaneously), from the linear sum of the two separate sensory evoked potentials, is typically used as an indication that these two processes interact with each other, thereby indexing multisensory interaction (Brandwein et al., 2011; Brett-Green, Miller, Gavin, & Davies, 2008; Foxe et al., 2000). However, multisensory interactions in the sensory processing stream might relate to processes that serve different functions (e.g. temporal facilitation, reliability-weighting). Several studies that assessed the neural basis of multisensory integration via a comparison of the summed and simultaneous evoked potentials have, in fact, reported interactions at different stages

of the processing stream. Some of these occurred as early as 50ms (e.g. Foxe et al., 2000) while others only started at mid-latencies around 100ms or even 200ms post-stimulus (e.g. Brandwein et al., 2011; Butler, Foxe, Fiebelkorn, Mercier, & Molholm, 2012). While most of these studies have assessed multisensory temporal facilitation, this thesis focusses on reliability weighting of object-based information and therefore requires a more temporally-refined hypothesis that is supported by the literature. A few recently published studies allow us to narrow down our predictions to assess the neural correlates of reliability-weighting by using computational approaches to model the hierarchy of multisensory processes (Boyle, Kayser, & Kayser, 2017; Rohe, Ehlis, & Noppeney, 2019; Rohe & Noppeney, 2015). Based on their findings of neural markers of sensory and perceptual weights at mid-latencies and at higher order processing areas we can derive predictions about processing differences between those individuals that integrate information optimally (sighted adults and early blind adults) and those that do not, or not yet (late-blind adults and sighted adolescents). A group of sighted adolescents aged 12-17 years was included as they contribute a developmental reference against which multisensory processing in the blind can be compared. That is, the brain of sighted adolescents can provide a snapshot of multisensory processing around the time at which late-blind individuals lost their sight, but before optimal multisensory integration emerged. By comparing processing of late-blind adults with sighted adults and sighted adolescents, we can gain a better understanding of which processing changes are due to maturational brain development and which are due to reorganization in response to blindness. Up to now, the development of the neural basis of audio-haptic multisensory integration has not been investigated. The inclusion of sighted adolescents furthermore allowed me to assess whether the neural basis of adult-like multisensory integration precedes the emergence of optimal performance on the behavioural level, or whether the transition from sub-optimal to optimal multisensory integration shares more similarities with sensory dominance processing.

Since the neural basis of audio-haptic integration using active touch has not been investigated before, this study further provides a benchmark for future studies to compare multisensory processing in other clinical populations such as individuals with autism, attention deficit hyperactivity disorder, or other sensory impairments such as hearing impairments. To do so, we provide a data-driven assessment of multisensory interactions across a time course of 600ms post-stimulus. This time period has been shown to encompass important neural markers that reflect both sensory as well as perceptual decision processes (Mostert, Kok, & de Lange, 2016).

As the following study entails several hypotheses that are based on the relative differences between groups, I include a table below to allow the reader to compare these to the results and findings more easily.

Reference Comparison	Sighted adults Multisensory interaction effects with onset between 204-252ms at higher				
Sighted	Order processing sites Weaker effect at similar latencies				
adolescents	Similar topography (unisensory) Different topography (multisensory)				
Early-blind adults	Similar effects at similar latencies Different topography (unisensory) Different topography (multisensory)				
Late-blind adults	No effects at similar latencies Similar topography (unisensory) Different topography (multisensory)				

Statement of Authorship

This declaration concerns the article entitled:								
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Neural correlates of audio-haptic integration in sighted and nonsighted individuals

Meike Scheller¹, Michael J. Proulx¹, Michelle de Haan², Annegret Dahlmann-Noor^{3,4}, Karin Petrini¹

¹Department of Psychology, University of Bath; ²Developmental Neurosciences Programme, University College London, London, UK; ³ NIHR Biomedical Research Centre Moorfields; ⁴Paediatric Service, Moorfields Eye Hospital, London, UK.

Corresponding author: m.scheller@bath.ac.uk

Abstract

Previous research suggests that optimal integration of active touch and sound information emerges late in childhood, between 13 and 17 years of age, and depends on sensory consistency during the first 8-9 years of life. Late-onset blindness, but not early-onset blindness, leads to impaired audio-haptic integration, however, the neural mechanisms that support this process remain largely unknown. Here, we examine the differences in audio-haptic multisensory processing between sighted and non-sighted individuals using high-density recordings of uni- and multi-sensory event-related potentials. We assessed event-related potentials for a group of 29 sighted adults, 12 sighted adolescents, five early-blind adults and three late-blind adults while actively tapping objects of different sizes and/or listening to the produced impact sound. Individual uni- and multi-sensory thresholds were previously measured thus allowing for comparison between groups that could integrate optimally and those that could not. We identified neural correlates of audio-haptic integration between 240-315ms in sighted adults and between 200-290ms in early-blind adults at frontal electrode sites. Interestingly, while this was achieved through response enhancement in the sighted, the early blind showed a response suppression, suggesting that optimal integration is achieved through different mechanisms in these groups. Sighted adolescents that are transitioning to optimal integration showed multisensory interactions at a later time window between 315-435ms, and with a more posterior distribution, indicative of sensory dominance. Notably, late-blind individuals showed no correlates of multisensory integration at similar time windows, which was evidenced by an absence of global activation enhancement. Furthermore, this group showed alterations in unisensory processing of touch and sound that could not be attributed to perceptual maturation within adolescent development. Taken together, these findings shed light onto the neural mechanisms underlying the development of optimal audio-haptic integration. Furthermore, they suggest a critical period for the development of optimal multisensory integration around the age of 8-9 years, during which availability of sensory input determines how the brain weighs sensory information later in life.

Introduction

All our daily interactions with the world around us depend on a meaningful interpretation of our environment. It is therefore crucial that our brain uses sensory information in an efficient way to construct accurate internal representations of the external environment. Within the last few decades a large body of behavioural and neurophysiological literature has established that the way in which the sighted adult brain combines multisensory information follows the principles of statistical optimality and thereby leads to a reduction in sensory uncertainty (Ernst & Banks, 2002; Fetsch, Pouget, DeAngelis, & Angelaki, 2011; Helbig & Ernst, 2007). Behaviourally, this results in a facilitation of stimulus detection (Gillmeister & Eimer, 2007), speeding up of reaction times (Sperdin, Cappe, Foxe, & Murray, 2009; Ulrich & Miller, 1997), or an increase in perceptual precision and accuracy (Alais & Burr, 2004; Rohde, van Dam, & Ernst, 2016) that could not be predicted by the best sense alone, but by a weighted combination of the two senses. Despite the behavioural relevance of multisensory integration and our functional understanding of it, it is still unclear how this process develops and how it is affected by a lack of sensory input.

In a recent study, we showed that developmental consistency in visual experience plays a key role in non-visual multisensory integration (Chapter 3). We compared groups of adults and children with different levels of visual experience (early blind, late blind, low vision and typically sighted) on an audio-haptic integration task to assess whether they integrate multisensory information in a statistically optimal fashion. Interestingly, while early-blind adults, and those with low vision, integrated audio-haptic information statistically optimally, similar to typically sighted adults, late-blind individuals showed an impairment in integration. The distinction between 'early' and 'late' blindness was based on previous findings suggesting that during the first 8 years of life the senses calibrate each other (Cappagli, Cocchi, & Gori, 2017; Gori, Sandini, Martinoli, & Burr, 2010) and that multisensory integration including the visual sense does not emerge before 8 years of life (Adams, 2016; Gori, Del Viva, Sandini, & Burr, 2008; or see Fig. 8 in Chapter 3). Currently, it is still unknown how these behavioural differences among sighted and non-sighted individuals in audio-haptic optimal integration reflect differences in neural processing, as previous literature has either focused on developmental changes of the single senses (Leclerc, Saint-Amour, Lavoie, Lassonde, & Lepore, 2000; Röder et al., 1999; Sadato et al., 1996), or assessed the influence of attentional selection on

competing multisensory input (Hötting, Rösler, & Röder, 2004; Kujala et al., 1995). For example, two studies that assessed auditory attention via a modulation of auditory evoked potentials compared typically sighted with congenitally-blind (Röder et al., 1999) and late-blind adults (>9 years; Fieger, Röder, Teder-Sälejärvi, Hillyard, & Neville, 2006). They found that, while both early- and late-blind individuals performed better than sighted controls, the late blind achieved this via an attentional modulation of auditory potentials at late latencies (coinciding with the P3 at 300-500ms), while the early blind showed attentional modulations of evoked potentials at earlier latencies (coinciding with the N1 at 100-200ms). The authors therefore suggested that, while early-blind individuals experience adaptations at the sensory-perceptual level, late-blind individuals achieve a similar increase in performance through cognitive mechanisms that are associated with target discrimination and recognition. Notably, while the role of attention as a prerequisite for optimal multisensory integration has long been debated, recent studies suggest that top-down attention is indeed involved in those perceptual processes that govern reliability-weighting (Boyle, Kayser, & Kayser, 2017; Busse, Roberts, Crist, Weissman, & Woldorff, 2005; Hötting et al., 2004; Vercillo & Gori, 2015).

What this might reflect is a differential cortical reorganization between early- and late-blind individuals, depending on the age at which vision was lost. This is corroborated by a number of studies showing wide-ranging differences in structural and functional connectivity between early- and late-blind, and typically sighted individuals (Bedny, Pascual-Leone, Dravida, & Saxe, 2012; Cohen et al., 1997; Cohen et al., 1999; Collignon et al., 2013; Ortiz-Terán et al., 2016). These studies show that higher order multisensory networks are mostly affected by compensational reorganization that takes place during late childhood and early adolescence, when vision is lost during adolescence or later (Ortiz-Terán et al., 2016, 2017). This is also in line with earlier research highlighting that brain maturation follows critical periods during which long-lasting cortical networks, that govern perceptual processes, develop (Gogtay et al., 2004; Sadato, Okada, Honda, & Yonekura, 2002). If these perceptual networks have developed under the influence of normal visual input, the brain retains only a reduced capacity to reorganize in order to compensate for a loss of vision that occurs later in development (Sadato et al., 2002). This would suggest that for individuals, who lost their sight early in life, compensation can be achieved through reorganization of sensory processing areas, allowing compensation at early processing stages. If sensory processing is enhanced due to reorganization in this group, audio-haptic integration might even take place at earlier processing latencies compared to sighted individuals. Those individuals that lost their sight after the initiation of multisensory network maturation, on the other hand, may achieve compensation through higher-order cognitive processes, which likely involve attentional regulation. Given the findings of a delayed compensation in late-blind adults (Fieger et al., 2006), multisensory integration would be expected to take place at later sensory processing stages. Furthermore, late-blind individuals might show a similar spatial distribution of sensory processing as sighted individuals of a comparable age to when they lost their vision (e.g., a person that lost their sight at 12 years of age would likely show a similar spatial distribution of unisensory processing to an 12 year old sighted child).

Although no study has so far examined the neural correlates of non-visual optimal multisensory integration in non-sighted individuals, several studies have assessed neural correlates of audio-visual or audio-tactile interactions in sighted adults and children. As the age of blindness-onset seems to influence the ability to integrate audio-haptic information, its development in typically sighted individuals can offer insights into the mechanisms leading to the integration impairment that is suggested in late-blind adults. In typically sighted adults, multisensory integration has been documented at several processing stages along the cortical hierarchy, starting with early effects (<100ms) in lowlevel sensory processing areas (Foxe et al., 2000; Kayser, Petkov, Augath, & Logothetis, 2005; Murray et al., 2005; Sperdin et al., 2009; see De Meo, Murray, Clarke, & Matusz, 2015 for a review), followed by mid- and late-latency effects (>100ms) at higher order processing areas (Bernasconi et al., 2018; Boyle et al., 2017; Brandwein et al., 2011; Murray et al., 2005). These multisensory interactions have been typically determined by a deviation of multisensory evoked potentials from the linear sum of unisensory evoked potentials. Several studies assessing the development of multisensory integration in sighted children, adolescents, and adults reported similar mid-latency effects (Brandwein et al., 2011; Brett-Green, Miller, Gavin, & Davies, 2008; Brett-Green, Miller, Schoen, & Nielsen, 2010; Russo et al., 2010). For example, Brandwein et al. (2011) measured eventrelated potentials during an audio-visual integration task and found that audio-visual facilitation, indicated by a speeding up of reaction times during multisensory presentation, approached adult-like levels at the age of 14 years. This multisensory facilitation was significantly correlated with a transition from sub- to super-additive responses at the fronto-centrally focussed N1 around 100-120ms. Furthermore, they demonstrated multisensory interactions at later time windows around 190-240ms, coinciding with the fall of the P2. These were more widespread in higher-order processing areas among adults, but less prevalent and more locally focussed in children and adolescents. A different study using a passive audio-tactile integration paradigm with sighted children aged between 6-13 years found that multisensory interaction effects were apparent within several time windows between 120ms and 300ms, largely coinciding with the P2 and N2 components, but also at later time windows between 400ms and 450ms (Russo et al., 2010), suggesting the involvement of regulatory control-mechanisms in governing multisensory integration.

These ERP studies suggest that multisensory integration is not a unitary process that takes place at a single time point, but is a complex process that requires both bottomup as well as top-down processes (Rohe, Ehlis, & Noppeney, 2019; Rohe & Noppeney, 2015). A few recent studies have used computational modelling approaches to combine psychophysical with neurophysiological data in order to increase our understanding of the different stages of multisensory integration along the sensory processing hierarchy. They showed that, while sensory weights influenced evoked neural responses at relatively early latencies (around 84ms), perceptual weighting could only be detected at midlatencies (>120ms; Boyle et al., 2017), and in higher-order processing areas (Boyle et al., 2017; Rohe et al., 2019; Rohe & Noppeney, 2015). They concluded that multisensory interactions, measured as the difference between simultaneous and summed unimodal potentials, at different latencies serve different functions (Rohe & Noppeney, 2015, 2018). While early multisensory interaction effects (Brett-Green et al., 2008; Foxe et al., 2000; Murray et al., 2005) likely reflect multisensory facilitation allowing for faster processing of multisensory information and lead to a speeding of reaction times, the integration into a reliability-weighted percept is only reflected at later processing stages and in higher order processing structures including the frontal (Cao, Summerfield, Park, Giordano, & Kayser, 2019; Noppeney, Ostwald, & Werner, 2010) and parietal regions (Rohe et al., 2019; Rohe & Noppeney, 2015). These studies have largely focused on audio-visual integration paradigms in sighted adults. Interestingly, Boyle et al. (2017) showed that sensory weights of visual information emerged at earlier latencies (84ms) than auditory weights (156ms), while only later in the trial, both visual and auditory weights were present at the same time (252-276ms). Furthermore, perceptual weights were present within two time windows, once between 120-132ms and once between 204-228ms. Notably, optimal multisensory integration is typically characterized by perceptual improvements that are larger than could be predicted by either of the unimodal senses.

Furthermore, another recent study found that fusion of reliability-weighted sensory input occurred from 220ms onwards (Cao et al., 2019). Therefore, we expect that optimality of multisensory integration can be detected during the later latencies reported by Boyle et al. (2017) and Cao et al. (2019), with an onset between 204ms and 252ms, that is, when sensory and perceptual weights of both modalities are present.

With the present study we aimed to examine, for the first time, the neural correlates of audio-haptic integration in sighted and non-sighted individuals. Specifically, we aimed to examine whether the audio-haptic integration impairment we found in lateblind, but not in early-blind individuals (Chapter 3) reflects differences in neural mechanisms of multisensory integration. To do so, we measured auditory, haptic and audio-haptic evoked potentials of sighted, early-blind and late-blind adults while performing a size perception task. As the age of blindness onset in late-blind individuals falls into a later stage of perceptual development which takes place during early adolescence (Cappagli et al., 2017; Chapter 3), we further assessed multisensory interactions of late-blind adults with both sighted adults and sighted adolescents, we can assess whether multisensory processing in late-blind adults is more similar to either group. This would allow us to disentangle whether sensory experience, rather than perceptual maturation during adolescence accounts for the neural processing differences in late-blind and sighted adults.

Based on the available evidence from studies assessing optimal multisensory integration in sighted adults (e.g., Boyle et al., 2017; Cao et al., 2019), we expected to find markers of optimal audio-haptic integration at later latencies, with an onset between 204ms and 252ms, and in higher order processing areas (frontal or centro-parietal sites) in typically sighted adults. In sighted adolescents, on the other hand, who are in the process of transitioning from sensory dominance (Gori et al., 2008; Scheller, Garcia, Bathelt, de Haan, & Petrini, 2019) to optimal multisensory integration (Nardini, Bedford, & Mareschal, 2010; Petrini, Caradonna, Foster, Burgess, & Nardini, 2016; Chapter 3), we predicted to find similar multisensory integration effects, however with weaker amplitudes (based on Brandwein et al., 2011) and with a more posterior distribution. The latter prediction derives from the findings of Russo et al. (2010) showing audio-tactile multisensory effects in more posterior regions in children (however, no adults were tested in their study), as well as studies showing that frontally-focussed higher order cognitive

networks that involve attentional modulation of multisensory information develop rather late (Gogtay et al., 2004; Ortiz-Terán et al., 2016). In the early blind, we predict to find multisensory modulations of event-related potentials at mid-latencies and higher-order processing areas, similar to sighted adults. This is because both groups benefit perceptually from integrating audio-haptic information optimally (Chapter 3). However, given the more pronounced cortical reorganization of low-level sensory processing substrates in the early blind (Collignon et al., 2013), we expect a different topographical distribution of unisensory processing activity in early blind compared to sighted adults. Finally, as we found an impairment of audio-haptic integration in the late-blind adults (see Chapter 3) we predict an absence of multisensory modulations in higher order processing areas at mid-latencies in this group. However, based on the findings that perceptual disadvantages in late-blind individuals might be compensated by higher-order cognitive mechanisms, taking place at later-latencies in the processing stream (Fieger et al., 2006), we expected to find modulations in multisensory processing at later latencies. Furthermore, given an increased reorganization in multisensory networks during late childhood/early adolescence (Ortiz-Terán et al., 2017), during or after which late-blind participants lost their sight, we expected the spatial distribution of sensory processing in late-blind individuals to be similar to that of sighted individuals, while the processing of multisensory integration for the late-blind individuals would differ from the other groups..

Methods

Participants

A sample of 29 sighted adults (15 female; 41.8 ± 19 years of age; 27 right handed) and 12 sighted adolescents aged 12-17 years (seven female; mean age 13.8 ± 1.7 years; nine right handed), who had normal or corrected-to-normal vision, participated in the experiment. All participants reported being neurologically healthy and not having any hearing or other sensorimotor impairments. Based on the individuals' perceptual performance measured in Chapter 3, that showed audio-haptic integration becomes more adult-like during adolescence, we focused on adolescents instead of younger children, as much less is known about the neural changes within this transitional period. We included adults with a large age range (19-70 years) in the present study to provide a more representative measure of the neural basis of audio-haptic integration in adulthood. The grouping of this

large age range is also supported by our findings showing that younger (18-44 years) and older (45-70 years) adults integrate audio-haptic information in a similar fashion (see Chapter 3).

Additionally, 8 blind adults (two female; 38.3 ± 19 years of age; all right handed) took part in the experiment. Out of these, five participants became blind within the first eight years of life (early blind), while three individuals became blind after the age of eight (late blind). Blindness was defined in line with the World Health Organization if participants possessed residual visual function with a visual acuity of logMar > 1.5 (World Health Organization, 2018). Levels of blindness were confirmed by medical records. Participant details for both sighted and blind participants can be found in Tables 1 to 3.

With the exception of two typically sighted adults, all participants took part in a previous behavioural task in which we assessed their individual audio-haptic integration performance and thresholds (Chapter 3). Due to a technical error during data collection, data from one blind individual (VI5) was not recorded. Handedness was assessed using the Oldfield Edinburgh Handedness Questionnaire (Oldfield, 1971). Prior to taking part, written, informed consent was obtained from all adult participants or parents/guardians of adolescents. Participants under the age of 18years further gave informed assent to indicate their interest in taking part in the research. Blind individuals were recruited through Moorfield's Eye Hospital, Bristol Eye Hospital, charity organizations for the blind as well as word of mouth. Sighted adults and adolescents were recruited through the University of Bath Community Research Participation Panel, University advertisements, one local school, and word of mouth. The experiment was performed in accordance with the Declaration of Helsinki and received ethical approval from the University of Bath Ethics Committee (ref # 15-211) and the National Health Research Authority (IRAS ref # 197917).

Participant	Sex	Age	Handedness	Group	Integrated optimally*	Bimodal Threshold (rounded)	Stimulus sizes
A01	Female	19	Right	Sighted adults	Yes	1mm	48mm, 50mm
A02	Female	20	Right	Sighted adults	Yes	1mm	48mm, 50mm
A03	Male	20	Right	Sighted adults	No	4mm	45mm, 53mm
A04	Male	20	Right	Sighted adults	Yes	3mm	46mm, 52mm
A05	Male	21	Right	Sighted adults	Not assessed	NA	47mm, 51mm
A06	Male	21	Right	Sighted adults	No	2mm	47mm, 51mm
A07	Female	23	Right	Sighted adults	No	4mm	45mm, 53mm
A08	Male	24	Right	Sighted adults	Yes	1mm	48mm, 50mm
A09	Male	26	Left	Sighted adults	Yes	2mm	47mm, 51mm
A10	Male	26	Right	Sighted adults	No	3mm	46mm, 52mm
A11	Female	27	Right	Sighted adults	Yes	2mm	47mm, 51mm
A12	Male	27	Right	Sighted adults	No	3mm	46mm, 52mm
A13	Female	30	Right	Sighted adults	No	2mm	47mm, 51mm
A14	Female	30	Right	Sighted adults	Yes	1mm	48mm, 50mm
A15	Male	33	Right	Sighted adults	Not assessed	NA	47mm, 51mm
A16	Female	50	Right	Sighted adults	No	2mm	47mm, 51mm
A17	Female	51	Right	Sighted adults	Yes	1mm	48mm, 50mm
A18	Female	55	Right	Sighted adults	No	2mm	47mm, 51mm
A19	Male	57	Right	Sighted adults	Yes	2mm	47mm, 51mm
A20	Female	58	Right	Sighted adults	No	4mm	47mm, 51mm
A21	Female	58	Right	Sighted adults	Yes	2mm	47mm, 51mm
A22	Female	60	Right	Sighted adults	No	2mm	47mm, 51mm
A23	Male	61	Right	Sighted adults	No	2mm	47mm, 51mm
A24	Male	63	Left	Sighted adults	Yes	2mm	47mm, 51mm
A25	Female	64	Right	Sighted adults	No	2mm	47mm, 51mm
A26	Male	65	Right	Sighted adults	No	2mm	47mm, 51mm
A27	Female	66	Right	Sighted adults	Yes	3mm	46mm, 52mm
A28	Female	68	Right	Sighted adults	Yes	2mm	47mm, 51mm
A29	Male	70	Right	Sighted adults	Yes	2mm	47mm, 51mm

Table 1: Demographic information of typically sighted adult participants.

Partici- pant	Sex	Age	Handed- ness	Group	Integrated optimally*	Bimodal Threshold (rounded)	Stimulus sizes
				Sighted			
C01	Female	12	Left	adolescents	No	3mm	46mm, 52mm
				Sighted			
C02	Female	12	Right	adolescents	No	4mm	45mm, 53mm
				Sighted			
C03	Female	12	Right	adolescents	No	3mm	46mm, 52mm
				Sighted			
C04	Female	13	Right	adolescents	No	4mm	45mm, 53mm
				Sighted			
C05	Male	13	Left	adolescents	No	3mm	46mm, 52mm
				Sighted			
C06	Male	13	Left	adolescents	Yes	2mm	47mm, 51mm
				Sighted			
C07	Male	13	Right	adolescents	No	2mm	47mm, 51mm
				Sighted			
C08	Female	15	Left	adolescents	No	2mm	47mm, 51mm
				Sighted			
C19	Female	15	Right	adolescents	No	3mm	46mm, 52mm
				Sighted			
C10	Female	15	Right	adolescents	Yes	3mm	46mm, 52mm
				Sighted			
C11	Male	16	Right	adolescents	No	3mm	46mm, 52mm
				Sighted			
C12	Male	17	Right	adolescents	Yes	2mm	47mm, 51mm

Table 2: Demographic information of typically sighted adolescent participants.

Table 3: Clinical and demographic information of visually impaired adults.

Participant	Sex	Age	Handed- ness	Age of Onset	Vision Status	Integrated optimally*	Bimodal Threshold (rounded)	Stimulus sizes
VI1	Female	18	Right	Birth	Early Blind	Yes	1mm	48mm, 50mm
VI2	Male	21	Right	Birth	Early Blind	Yes	2mm	47mm, 51mm
VI3	Male	59	Right	Birth	Early Blind	Yes	2mm	47mm, 51mm
VI4	Male	33	Right	5.5 Years	Early Blind	Yes	1mm	48mm, 50mm
VI5	Female	19	Right	7 Years	Early Blind	Yes	2mm	47mm, 51mm
VI6	Male	60	Right	10 Years	Late Blind	No	4mm	45mm, 53mm
VI7	Male	61	Right	11 Years	Late Blind	No	3mm	46mm, 52mm
VI8	Male	35	Right	25 Years	Late Blind	No	5mm	44mm, 54mm

*determined in Chapter 3

Stimuli

Haptic and auditory stimuli consisted of two 3D-printed balls, a big and a small one, and their corresponding sounds. The sounds were amplitude-modulated recordings of a medium-sized ball (average of the big and small ball, with 49mm in diameter), which was dropped on a resonating surface, creating an impact-like sound at the time of the tap. Amplitude of the sound was modulated using Praat software (Boersma, 2001) in a way, that the bigger ball created a louder sound, and the smaller ball created a quieter sound. Increment size for sounds was 0.5dB Sound Pressure Level (SPL) louder per 1mm bigger object size. Stimulus generation is described in more detail in previous studies (Petrini, Remark, Smith, & Nardini, 2014; Scheller et al., 2019). The size of the stimuli was adjusted to the individual's bimodal size discrimination threshold, which was assessed for each individual (see Chapter 3) and is reported in the participant demographics tables. The stimuli were chosen so that the difference equals twice the size of their perceptual discrimination threshold, and averaged to 49mm or 75dB in haptic size or sound amplitude, respectively. For example, if a participant was able to tell two stimuli with a size difference of 2mm/1dB apart (i.e. discrimination threshold of 2mm), the haptic stimuli for this participant were 47mm and 51mm (49mm \pm 2mm) in haptic size, and 74dB and 76dB in auditory amplitude, respectively. In the audio-haptic congruent condition these stimuli were paired by matching small sizes with low amplitudes (e.g. 47mm+74dB), and big sizes with high amplitudes (e.g. 51mm+76dB). In the incongruent condition, small sizes were matched with high amplitudes (e.g. 47mm+76dB) and vice versa (e.g. 51mm + 74dB). We used twice the discrimination threshold to ensure that participants were able to perceive a difference between the two stimuli, while keeping the task difficult enough so that integration can be more efficient and the conflict in the incongruent condition is kept to a minimum. As perceptual precision often differs between individuals, even when they share similar characteristics (e.g. sightedness, age), the adjustment of stimuli to individual thresholds is desirable in perceptual tasks whenever possible. For the two typically sighted adults, who did not take part in the previous study, the average bimodal discrimination threshold of the group (e.g. sighted adults) was assumed.

Stimulus presentation

Haptic stimuli were placed in the same location in front of the participant on a thin layer of foam, which was resting on a touch screen (model KTMT-1921, Keytec, Texas,

US, see also Petrini et al., 2014; Scheller et al., 2019). The thin foam prevented the haptic stimuli from creating any sounds when being placed on the touch screen and to mark the stimulus location for consistency. A thick semi-soft foam block was placed next to the touch screen allowing individuals to rest their dominant hand that executed the movement between trials. Sounds were played back through a single speaker (Logitech Europe S.A., Lausanne, model: z120) in front of the participant in a fixed position, approximately 7cm away from the haptic stimulus in the participant's mid-sagittal plane. Stimulus presentation was controlled using E-Prime. Event codes were sent to the EEG acquisition software whenever a tap was registered on the touch screen, which triggered the auditory stimulus to be played back. The temporal delay between the actual haptic tap and the auditory stimulus took around 80ms. This delay was due to information transmission time of the hardware and wiring infrastructure. However, as this delay fell right within the duration of haptic touch stimulation (contact with ball), this was highly unlikely to lead to a disruption of integration of the two senses. Indeed, slight asynchronies in the onset of causally related events, whereby a predicted effect (auditory tone) follows its cause (haptic tap) within 200ms does not disrupt perceived simultaneity and thereby sensory fusion (Rohde, Scheller, & Ernst, 2014; Toida, Ueno, & Shimada, 2016). Lastly, no participant reported to perceive any asynchrony between the stimuli when asked at the end of the study. As the delay between the auditory trigger being sent and the sound being played was 24ms, as assessed by an auditory timing test, the delay was likely caused by the haptic stimulus presentation hardware and led to a delay of 56ms for the trigger transmission. As the haptic tap initiated each trial, all conditions were affected similarly, and the offset could be added for all conditions during EEG processing. Effectively, for the task at hand this meant that the initial tap occurred earlier than the onset of the sound, to which ERPs were time-locked. Therefore, any major deviations from baseline before Oms in the bimodal condition likely reflect haptic processing rather than any multisensory effects. Data acquisition was conducted in NetStation 5 (Electrical Geodesic Inc., OR). Off-line pre- and post-processing was conducted in Matlab (The Mathworks, Inc., Natick, MA) using the EEGLAB toolbox (Delorme & Makeig, 2004), and custom routines that are described in the EEG processing section.

Stimuli were presented in four different conditions, all of which were completed by all participants. In two conditions, only haptic or auditory information was presented (hereafter: 'auditory only', 'haptic only'). In the other two conditions, both haptic and auditory information were presented simultaneously, once in a congruent, and once in an incongruent pairing ('bimodal congruent', 'bimodal incongruent'). In the bimodal congruent condition, the balls were presented with its corresponding sounds (e.g. big ball with louder impact sound). In the incongruent condition, the big ball was presented with the sound of the small ball (quieter sound), and vice versa. All conditions were arranged in blocks, which were presented in a counterbalanced order across participants. At the beginning of each block, participants were presented with two "example" stimuli from the respective condition and were asked whether they could tell which one was bigger in order to confirm that they were able to perceive a difference between them. One block consisted of 40 repetitions whereby each size was presented 20 times in a semi-randomized order. The participants were given short 2-4 minute breaks between the blocks to allow them to rest and to receive the instructions for the next block.

Procedure

Participants were seated in a comfortable chair in front of the set up in an electrically shielded room (see Figure 1). They were blindfolded throughout the whole experiment and rested their dominant hand on a semi-soft foam block in front of them. At the beginning of each trial (except during auditory only trials), the experimenter placed one of the two balls in the stimulus presentation location on the touch pad and guided the participant's hand to the object. Participants then gave the ball a brief but firm tap, while keeping their hand straight and flat. This was important in order to decrease the information gained from other haptic cues like curvature. Once the object was tapped, pressure was sensed on the touch screen and triggered the sound to be played back through a speaker installed next to the stimulus (except in the haptic only condition). The timing of the sound coincided with the longer duration of the tapping movement. After tapping the ball once, the hand was returned to the resting position and the next trial started.

In the haptic-only block participants tapped the ball without hearing the auditory stimulus at the same time. During the audio-only condition, participants were given a pen with which they had to tap on the touch pad, which then triggered the sound to be played back. As participants were blindfolded throughout all blocks, the experimenter guided their hand to the stimulus presentation location. This allowed maintaining the same movement throughout the different conditions and to reduce cognitive load of participants towards the task-irrelevant stimulus location. Participants were instructed to focus on the size of the object, conveyed through all the senses available, that is, hearing, touch, or

both at the same time. They were naïve about the amount of different sizes (two, one big and one small one) within each block as well as the congruency modulation in the incongruent condition. In order to make sure participants' attention was focussed on object size, they were asked to report how many different object sizes were presented at the end of each block. Counting objects based on certain features, such as size, requires participants to have an accurate estimate of that feature, which is facilitated by integrating multisensory information when it is available.



Figure 1: Experimental set up. Blindfolded participants were seated in front of the set up in a quiet and electrically shielded chamber. In between trials, their dominant hand rested on a semi-soft foam block (a). Stimuli were placed, one at a time, on a touch screen (b) in front of the participant. The experimenter guided the participant's hand to the stimulus, to allow them to briefly tap it. Once pressure was registered on the touch screen, the matching sound (bimodal congruent) or the non-matching sound (bimodal incongruent) was played back through a speaker (c) positioned closely to the stimulus. In the 'auditory only' condition, the tap was elicited by tapping on the touch screen with a pen. In the 'haptic only' condition, the tap was recorded but no sound was played back. Stimulus presentation was controlled by the experimenter who received instructions for a counterbalanced presentation on a screen. The EEG signal was amplified and recorded by the acquisition machine outside the shielded cage which received event information from the stimulus control machine.

EEG acquisition

Continuous EEG was recorded using a high density, high-impedance EGI (Electrical Geodesics Inc., OR) system, with a HydroCel Geodesic Sensor Net with 64 Ag/AgCl electrodes, and a NetAmps 400 amplifier with anti-aliasing filter and a sampling rate of 1000Hz. Electrode spacing is based on geodesic tessellation of the head, that is, electrodes are placed in a way to achieve the shortest distance between them on the head surface, leading to a good coverage of the electrical field at the head surface. They are held in place with a tension structure made of elastic polymer threads. Recordings were online referenced to central electrode Cz. Electrode impedance was monitored and adjusted before each session to keep impedances below $50k\Omega$.

EEG pre-processing

Raw EEG files consisted of continuous recordings for each block and each participant separately. For pre-processing, all four condition files were merged into one subject file and all following steps were conducted on merged, subject-specific files. This was done to allow for a better component extraction during ICA as the efficacy of ICA is heavily dependent on the amount of data it trains on. Pre-processing steps are depicted in Figure 2. First, data was down sampled to 256Hz and the age appropriate montage was selected to guarantee better accuracy in later processing steps such as channel interpolation. Signals were filtered between 0.1Hz and 40Hz using a Hamming windowed sinc FIR filter. The low pass filter was applied to reduce the effects of movement-related high-frequency noise. As the noise level as well as condition-effects at the reference channels can strongly affect the overall signal quality (Luck, 2005), the signal was rereferenced offline to the average of the left and right mastoid electrodes. Mastoids were chosen over the average reference as to reduce the likelihood of movement artefacts contaminating the signal. Another advantage of an average mastoid reference is to reduce group-specific effects that result from increased posterior alpha power in sighted participants with closed eyes (Barry, Clarke, Johnstone, Magee, & Rushby, 2007; Barry & De Blasio, 2017) compared to blind participants. Bad channels were rejected based on three criteria: firstly, channels that exceeded a normed joint probability threshold of 3 standard deviations were removed as they are indicative of highly improbable signals (see Gabard-Durnam, Mendez Leal, Wilkinson, & Levin, 2018). Next, defect channels were detected by assessing correlation between neighbouring channels and removing channels with low correlation of $r \le 0.6$. Lastly, we deselected channels in the periphery for later pre-processing due to their high likelihood of incorporating movement artefacts and noise, reducing the quality of ICA decomposition. Data at channels that were removed at this stage were interpolated from neighbouring channels after Independent Component Analysis (ICA). Next, artefact rejection was performed through spectral thresholding of contiguous portions of data using EEGLab's pop rejcont function (Delorme, 2009) with an upper threshold of 8 dB for 20-40Hz and 6dB for 23-25Hz. EEG recordings were time locked to the onset of the sound and segmented into epochs of 700ms length, starting at -100ms pre-stimulus to 600ms post-stimulus onset. We chose to time-lock the signal to the sound rather than the haptic tap as the exact onset and duration of the sound is more consistent compared to active touch. That is, the time duration and onset of the sound are fixed and can be determined with millisecond precision, while active haptic perception naturally bears more variability in both the duration of stimulus exposure and the intensity of pressure upon impact. In a previous study using the same set-up we showed that timelocking to the auditory stimulus yields reliable results (Scheller et al., 2019). Before segmenting the signals into epochs, relative to the onset of the sound, the temporal offset between the ball tap and the onset of the sound were corrected for by subtracting the difference of 56ms from the time point at which the ball tap was registered at the stimulus presentation machine. A joint probability criterion was applied on the epoched signal to detect epochs with unusually peaky distributions, which are likely to represent artefacts (Delorme, Sejnowski, & Makeig, 2007). That is, epochs that showed activity lying outside of 3.2 standard deviations of the joint probability at both local and global level were rejected. Finally, to eliminate sinusoidal noise and artefacts related to eye movements or noisy electrodes, the epoched data were submitted to an Independent Component Analysis (ICA) implemented in EEGLAB (Delorme & Makeig, 2004). Following the removal of components related to muscular movement and strong sinusoidal noise, data from previously deselected channels were replaced using spherical spline interpolation (Perrin, Pernier, Bertrand, & Echallier, 1989) based on their neighbouring channels. Finally, we applied baseline correction on the 100ms pre-stimulus to correct for any signal offset. Single-subject ERPs were created by averaging singletrial epochs for each participant and condition separately.



Figure 2: Schematic of EEG pre-processing pipeline

Data analysis

We conducted two analysis steps to assess the neural correlates of multisensory integration processes in the four participant groups (sighted adults, sighted adolescents, adults that went blind before the age of 8 years and those that went blind after the age of 8 years). Note that the early-blind adults showed optimal integration of auditory and haptic information in a previous study (Chapter 3), in stark contrast to the late-blind adult group, who did not show signs of a multisensory integration benefit. The two analysis steps included (1) identifying topography-dependent, local effects of audio-haptic integration at three electrode sites along the head midline and (2) determining global indicators of audio-haptic integration via a reference-free, location-independent measure.

For both analysis steps we compared the algebraic sum of unimodal potentials from the auditory-only and haptic-only conditions (A+H) with the potentials of the bimodal congruent condition (simultaneous presentation, AH) by subtracting amplitudes of the latter from amplitudes of the former, i.e. $\Delta = (A + H) - AH$. As the algebraic sum of the unimodal potentials would be equivalent to an independent processing of auditory and haptic information, deviations of the bimodal potential from the summed unimodal potential ($\Delta \neq 0$) is indicative of multisensory interactions. This approach has typically been used for assessing multisensory interactions at the neural level in several previous audio-tactile (Bernasconi et al., 2018; Foxe et al., 2000; Murray et al., 2005) and audiovisual (Brandwein et al., 2011; Giard & Peronnet, 1999; Teder-Sälejärvi, McDonald, Di Russo, & Hillyard, 2002) ERP studies. We further compared potentials between congruent and incongruent stimulus presentations. However, as the main focus of this paper is on the integration of sensory information into an optimally weighted percept, instead of conflict detection, this analysis is available in the Supplementary Material S1.

(1) *Identifying local effects of audio-haptic integration at three electrode clusters in all participant groups.* Based on previously reported findings of audio-tactile interactions in sighted adults and children (Brandwein et al., 2013, 2015; Brett-Green et al., 2008; Davies, Chang, & Gavin, 2010), we selected three regions of interest along the brain's sagittal plane at midfrontal, central, and midparietal sites. Notably, several recent reports suggest the involvement of a fronto-parietal control network in the sensory weighting of multisensory integration (Cao et al., 2019; Noppeney et al., 2010; Rohe & Noppeney, 2015). High-density recording with 64 electrodes allowed us to obtain a measure that is
less influenced by local disturbances and noise by averaging the signal at two (midfrontal, midparietal) or seven (central) electrode sites into clusters.

In order to identify local effects of audio-haptic integration along the midline, we (a) employed a data-driven selection of temporal windows, (b) assessed amplitude modulations at the identified time windows and (c) computed topographic representations of the main effects.

a. Time windows that showed multisensory interactions were determined by examining group-averaged difference waves. These were computed by subtracting the potentials of the bimodal congruent condition from the summed unisensory potentials for each participant separately, before creating groupaverages across all participants within each group. By comparing the amplitude of the difference waves against pre-stimulus baseline levels on a point-by-point basis using two-sided t-tests, we retrieved a t-statistic for each time point within the 700ms interval. To control for inflation of type I error as a result of multiple comparisons we applied a time stability criterion that takes the dependence of our measurement across time and space into account (Guthrie & Buchwald, 1991; Picton et al., 2000). That is, depending on the number of participants, the amount of time points that were compared (n = 181) and autocorrelation within the group data, a cut-off value was calculated for each participant group and electrode cluster separately. This cut-off indicated the minimum run-length of consecutive tests that had to exceed the group dependent critical t-value (sighted adults: 1.721; sighted adolescents: 1.782; early-blind adults: 2.015; late-blind adults: 2.92; based on alpha < .05) in order to be deemed significant. This run-length based correction procedure has been used repeatedly for significance testing of difference waves in previous multisensory ERP studies (e.g. see Butler, Foxe, Fiebelkorn, Mercier, & Molholm, 2012; Saint-Amour, De Sanctis, Molholm, Ritter, & Foxe, 2007; Scheller et al., 2019; Stekelenburg, Keetels, & Vroomen, 2018). This meant for sighted adults that at least 7 (midfrontal) or 11 (central & midparietal) consecutive t-tests had to yield a t-value that exceeded the critical value, in order to be deemed a significant effect. With a sampling rate of 256Hz this is equivalent to a time epoch of 28ms and 43ms respectively. For sighted adolescents, at least 7 (midfrontal & central) or 13 (midparietal), for early blind 5 (midfrontal & midparietal) or 10 (central) and for late blind 4 (all sites) consecutive time points had to indicate t-values exceeding group-dependent critical t.

- b. Once time windows with significant multisensory effects were identified, area amplitude measures were taken at these time windows and compared statistically using Bonferroni-corrected two-sided t-tests. Area amplitudes were calculated as the cumulative amplitude over the defined time-window that summed up the area under the curve in a polarity-sensitive fashion. That is, area amplitudes can take on negative values in cases where the deflection is negative. We chose to not report the cumulative absolute (polarity-insensitive) area as polarity deflection can yield more information about different neural mechanisms such as enhancement or suppression.
- c. To provide at least a crude measure for the localization of neural generators, topographical maps that show the voltage distribution across the scalp are provided for the time windows in which significant multisensory effects were identified. These maps were scaled relative to the maximum absolute activation within a certain time window for each group separately, to provide a more comparable overview of neural activation across the head surface.

(2) Determining global indicators of audio-haptic integration via a reference-free, location-independent measure. In order to provide a measure that is un-biased by experimenter selection of pre-determined electrode clusters and not influenced by between-group effects resulting from neural reorganisation, we identified temporal multisensory processing differences between the four participant groups using Global Field Power (GFP). This measure is equivalent to the standard deviation of momentary potential values across the headspace (Lehmann & Skrandies, 1980) and serves as a reference-free and topography-independent measure of neural activation over time. High GFP values indicate time points of high signal-to-noise ratio, and thereby high neuronal synchronization on the global level (Koenig & Melie-García, 2010; Murray, Brunet, & Michel, 2008). Due to differing neural generators affecting the variability of peak latencies between groups, we used GFP to assess neuronal activity between groups and to provide a measure that is both reference- and topography-independent. For this analysis step, we compare GFP strength between groups to index the presence or absence of high global synchronization, comparing audio-haptic congruent (simultaneous) with the summed audio and haptic presentation conditions. Thereby, we focussed on the peaks of high global activity that fell within the time-windows showing multisensory interactions

in the sighted and early-blind adults, that is, the two participant groups that integrate audio-haptic information optimally.

Results

To confirm whether individuals that were tested in the present study integrate multisensory information in a statistically optimal fashion we previously assessed the extent to which they perceptually benefit from having both sound and touch available at the same time. Multisensory integration results in a perceptual benefit that is equivalent to a reduction in sensory noise, and can be approximated by Maximum Likelihood Estimation (Gori, Sandini, & Burr, 2012; Rohde, van Dam, & Ernst, 2016). This assessment was done on a separate occasion and the results are presented in Chapter 3. Multisensory benefit in size discrimination, which is defined as the difference between bimodal discrimination threshold and the individual's predicted optimal performance for the subset of participants that participated in this study is indicated in Figure 3A. Lower values indicate a greater perceptual benefit when multisensory information is available, compared to unimodal information. Thresholds are representative of the larger group in Chapter 3, confirming that the subsample of participants in this study is unbiased. They indicate that sighted and early-blind adults integrate audio-haptic information in a statistically optimal fashion, while late-blind adults do not. Sighted adolescents are transitioning from sensory dominance to optimal integration, but the group tested here does not yet show the same integration benefit as adults.

To verify participants were paying attention to the stimulus size they were asked to report the number of object sizes they perceived within each block. This task was also used to make sure that participants did not assume differences in the stimuli between unimodal and bimodal conditions. That is, presentation of more than one cue at the same time (i.e. more information) might evoke the percept of a different amount of object sizes, compared to unimodal presentation. As indicated in Figure 3B there were no differences between conditions in the number of perceived stimulus sizes for all participant groups.



Figure 3: Panel A. Multisensory benefit in the present sample of participants, split by group. Lower values on the y-axis indicate a stronger perceptual benefit from multisensory integration, while higher values indicate less or no benefit. Dashed line at y = 0 indicates statistical optimality as predicted by maximum likelihood estimation. Error bars indicate 95% CIs. Panel B. Reported amount of different ball sizes for each participant group and condition separately. Error bars indicate 95% CIs.

(1) Local effects of audio-haptic integration at three electrode clusters

Grand average ERPs of auditory and haptic conditions are displayed for all four participant groups at midfrontal, central, and midparietal electrode clusters separately (Figure 4).

Auditory evoked potentials showed a clear P1-N1-P2 complex at CZ electrodes in both adolescents and adults, with earlier latencies of the P1 and N1 components in adults compared to adolescents, in line with previous reports of developmental changes in auditory processing (Gilley, Sharma, Dorman, & Martin, 2005). In adults, P1, N1 and P2 peaked at 72ms, 127ms, and 194ms, respectively. In adolescents, the peak latencies were 104ms, 139ms, and 194ms. Early-blind individuals showed a less pronounced P1, peaking at 92ms, and clear N1 and P2 components, peaking at 135ms, 206ms respectively. Late-blind adults showed similar latencies as early-blind adults, with P1 peaking at 92ms, a more prominent N1 at 143ms, and P2 peaking at 213ms. However, peak amplitudes of the P2 component were much less pronounced in this group compared to other groups. A pronounced N2 negative deflection at frontal and central sites can largely be observed in the adolescent group, while the N1 at central and parietal sites is more prominent in adults. The shift in negativity dominance of the N2 in children and adolescents up to the age of 16 years, towards a more pronounced N1 negativity in adults

has been repeatedly reported in previous investigations of the maturation of the auditory evoked potential (Ceponiene, Rinne, & Näätänen, 2002; Ponton, Eggermont, Khosla, Kwong, & Don, 2002; Ponton, Eggermont, Kwong, & Don, 2000). Similarly, the lateblind adults show a more pronounced negativity of the N2 at frontal and central sites, while the N1 is more similar to sighted adults. Overall amplitudes were lower in adults compared to adolescents, which is typically observed in developmental ERP studies, likely indicating synaptic pruning throughout development (e.g. Brandwein et al., 2011).

As ERPs are time-locked to the onset of the sound, which followed the haptic tap by around 80ms, and because we used active touch, the haptic-only grand average ERP shows earlier onset latencies and cannot be compared to the potentials following passive, somatosensory stimulation (e.g. Hötting et al., 2004). However, we still find components similar to those reported in the literature assessing audio-tactile integration (Brett-Green et al., 2008), shifted towards earlier latencies.



Figure 4: Grand average ERP waveforms for the auditory only (blue), haptic only (red) and bimodal congruent (green) conditions for all participant groups and three regions of interest: midfrontal (upper panels), central (middle panels) and midparietal (lower panels). Shaded error bars indicate one standard error of the mean.

Figure 5 shows the grand average ERPs of the summed unimodal and the bimodal congruent potentials for all participant groups at midfrontal, central and midparietal electrode clusters. In sighted adults we identified one time window at the midfrontal electrode cluster at which potentials to simultaneous audio-haptic stimulation significantly exceeded that of the summed unimodal response. This effect occurred at 240-315ms, coinciding with the late P2. Sighted adolescents showed two significant subadditive effects at midfrontal and central electrode sites, but at later latencies, between 315-435ms, coinciding with the peaking of the N2. Early-blind individuals showed several effects, both super-additive and sub-additive, starting from midparietal electrode sites at 100-150ms, followed by an interaction effect at all three electrode sites between 200-320ms. A later effect was noticed between 390-450ms at central and midfrontal sites, at similar times as sighted adolescents, however, with a super-additive compared to a subadditive effect. For late-blind individuals we identified only one time window in which potentials of the simultaneous presentations differed significantly from the summed unimodal potentials. This effect occurred at early latencies at 85-110ms. Here, the simultaneous potentials showed a prominent deflection indicative of the P1, however, this component was not present in either auditory or haptic conditions (see the summed unimodal potentials in Figure 5).



Figure 5: Grand average ERP waveforms of summed unimodal (purple) and simultaneous (green) potentials at three regions of interest: midfrontal, central and midparietal. Shaded error bars indicate the standard error.

Area amplitudes were measured for each identified time-window as outlined in the Methods section (Data Analysis 1b) and are depicted in Figure 6. In sighted adults, area amplitudes during the time window of 240-315ms were significantly larger at midfrontal sites in the simultaneous than summed unimodal potentials. The same was true for sighted adolescents at both midfrontal and central sites during a later time period (315-435ms). Early-blind individuals showed amplitude differences elicited by simultaneous bimodal stimuli at several time windows at all three electrode sites. Amplitudes were overall more negative for the simultaneous than for the summed potentials, leading to super-additive effects during the negative components (110-140ms; 390-440ms) and sub-additive effects during positive deflections (100-150ms; 200-320ms; 510-580ms). Similar to sighted adults and adolescents, late-blind adults showed significantly higher area amplitudes at midfrontal sites, however, during an earlier time window. For a summary of the main effects and statistical test results see Table 4.





Figure 6: Average area amplitudes of summed unimodal (purple) and simultaneous (green) stimulus presentation for the time windows identified previously at midfrontal, central, and midparietal sites. Error bars indicate standard error of the mean.

	Time period		Electrode	Effect		
Group	[ms]	Component	site	direction	Statistics	Effect size
Sighted adults	240 - 315	P2	Midfrontal	AH > A+H	t(21) = 3.70, p = .001*	0.54
Sighted adolescents	315 - 415	N2	Midfrontal	AH < A+H	t(11) = 2.64, p = .023*	0.56
	370 - 435	N2	Central	AH < A+H	t(11) = 2.51, p = .029*	0.70
Could blind	100 150	D1 /N1	Miduoviatal		t/2) - C 1C 000*	1 40
Early blind	100 - 150	P1/N1	iviluparietai	AH < / > A+H	$l(3) = 0.16, p = .009^{\circ}$	1.48
	110 - 140	N1	Central	AH > A+H	t(3) = 2.62, p = .079	0.98
	200 - 275	P2	Midfrontal	AH < A+H	t(3)=3.74, p=.033*	1.23
	200 - 290	P2	Central	AH < A+H	t(3) = 3.81, p = .032*	2.03
	220 - 320	P2	Midparietal	AH < A+H	$t(3) = 3.92, p = .029^*$	1.25
	390 - 450	N2	Central	AH > A+H	t(3) = 2.20, p = .115	1.22
	400 - 440	N2	Midfrontal	AH > A+H	t(3) = 6.72, p = .007*	1.82
	510 - 570		Central	AH < A+H	t(3) = 4.86, p = .017*	1.60
	535 - 580		Midfrontal	AH < A+H	t(3) = 2.99, p = .058	1.00
Late blind	85 - 110	P1	Midfrontal	AH > A+H	t(2) = 16.17, p = .004*	1.20
*significant after correction						

Table 4: Time windows for which significant multisensory effects of amplitude were identified within the different participant groups and electrode clusters.

To assess whether there are developmental changes in processing substrates and compensatory reorganization in the blind we compared the spatial distribution of multisensory interaction effects (summed minus simultaneous presentations) between the four groups (Figure 7). Colour intensity indicates the strength of neural activation differences between summed unimodal and simultaneous conditions across the headspace. Green indicates no difference between summed unimodal and simultaneous conditions, while warmer and cooler colours show positive (A+H > AH) or negative (A+H < AH) differences, respectively. Topographic maps are scaled to the strongest absolute difference within each time window. Labels of the closest electrodes (based on the international 10-20 system) to maximum activation are provided next to each topographic plot. Note that these plots indicate the difference between summed unimodal and simultaneous conditions, which can result from either unimodal or bimodal processing. Topographical plots for the two unimodal and bimodal condition are displayed for a selected time window around the P2 in Figure 9.

In sighted adults, the time window and amplitude assessment above showed amplitude modulations by multisensory stimuli at frontal electrode sites at 240-315ms, coinciding with the P2 component. The strongest difference in activation during this time period were left-lateralized and were registered at electrodes F7 and FP1, which map onto the left inferior frontal gyrus (IFG) and the left superior frontal gyrus (SFG; Okamoto et al.,

2004). In the sighted adolescent group, multisensory interactions were noted during later time windows at frontal and central sites, with peak activity in the left fronto-polar (FP1) area. Early-blind adults showed multisensory interaction effects during several time windows, starting at 100-150ms at midparietal sites and then at slightly later latencies between 200ms until 320ms at midfrontal, central and midparietal electrodes. The strongest amplitude effects were registered at right central (C4) and left frontal (F7) sites. Late-blind adults also showed difference maxima at fronto-central sites, however with a right lateralisation in contrast to the other three groups. Significant effects of multisensory interactions were found at early latencies at midfrontal electrode sites.



Figure 7: Difference topographies between simultaneous and summed unimodal conditions for all four participant groups. Topography plots display average voltage distributions of summed and simultaneous differences for the four time windows identified in the data driven time-window analysis. Warm colors show areas of higher activation for the summed unimodal than bimodal potentials, while colder colors indicate higher activation in bimodal compared to the summed unimodal conditions. All maps are color-scaled to the absolute maximum voltage of the respective time window and participant group. Black circled asterisks indicate the electrode site (midfrontal, central, or midparietal) for which significant differences were observed. Names of the closest electrodes according to the 10-20 system that showed maximum activation during the respective time windows are written next to topographical plots. Note that differences can result from either of the two unimodal or the bimodal conditions.

(2) Determining global indicators of audio-haptic integration via a reference-free, location-independent measure

To assess the differences in global activation across the scalp, Global Field Power (GFP) was calculated for the summed and simultaneous conditions for each individual separately before averaging it across individuals for every group. Visual inspection of GFP across the epoch range (see Figure 8) showed clear activation peaks throughout the epoch that corresponded largely to components N1, P2, and N2 (see Figure 5). In sighted adults, the strongest activity can be seen within 180-280ms, coinciding with the P2, while in adolescents this activity peak was much shorter and followed by an even stronger activity later in the epoch between 280-400ms. The latter falls in line with the more pronounced N2 of this age group. Early-blind adults showed, similar to adolescents, overall lower activation in the bimodal condition compared to the sum of the unimodal conditions, as well as three peaks in GFP, at around 120ms, 200ms, and 350ms. This fell in line with the N1, P2, and N2 components. Late-blind adults showed similar peak activations in time windows around the time of the P1 and P2 in the summed unimodal conditions. However, this group did not show any pronounced increases or decreases in global activation around the time of the P2 in the bimodal congruent condition. In sighted and early-blind adults, multisensory modulations of the P2 have been found in our previous analysis at frontal sites. To better understand the spatial distribution of this effect, and the contribution of the auditory and haptic modality, topographic maps were plotted at the peak times of global activation for all four groups and for all conditions separately (see Figure 9). Furthermore, the late-blind individuals showed another peak in the summed unimodal GFPs that was absent in the bimodal GFP at around 400-490ms.

In order to assess differences in global multisensory processing effects between the groups, we compared the GFP of summed unisensory and simultaneous conditions at the time of the P2, where multisensory modulations were found in sighted and early-blind adults. We used two measures to compare GFP deviations between unimodal summed and simultaneous conditions within a time window centring on the peak activation (+/-20ms). These were (1) rate of change and (2) correlation. The rate of change is used to provide a measure of the cumulative change in GFP within the time window, independent of signal latency. It is calculated as the cumulative sum of the absolute change in GFP

amplitude between each time point i and for each condition c separately, and can be expressed as:

$$RoC_{c} = \sum_{i=1}^{k} \left| \frac{GFP_{i} - GFP_{i-1}}{time_{i} - time_{i-1}} \right|$$

Strong differences in RoCs between both conditions indicate stronger differences in the dynamics of global activation as a result of multisensory stimulation. However, as the RoC measure is not sensitive to the directionality of changes (we calculated the cumulative absolute change to gain robustness against latency effects) within our defined time window, we used correlation as a second measure to assess polarity-sensitive similarity between both conditions. Correlation here describes the product moment correlation coefficient of the two GFP measures over the time windows of interest. The first time window encompassed 82ms, centring on the maximum GFP amplitude of the summed unimodal condition and were determined for each group separately. Peak GFP amplitudes occurred at 202ms, 196ms, 200ms, and 204ms for sighted adults, adolescents, early-blind, and late-blind individuals, respectively (see shaded regions in Figure 8). The second time window was only analysed in late-blind adults and encompassed global activation between 400-465ms (see second shaded region in bottom right panel).



Figure 8: Global Field Power in all four participant groups for summed unimodal (purple) and simultaneous bimodal (green) conditions. Shaded regions around 200ms indicate the time window of interest coinciding with the P2components during which multisensory interactions have been identified in the previous analysis. The second shaded region in the late blind group indicates second time window of interest at 400-465ms. Topographic plots show activity distribution of difference maps between summed and simultaneous activations within the shaded time window. Blue regions indicate higher multisensory activity, while red regions show higher activity in the summed unimodal conditions.

The absence of increased activation and deactivation for the bimodal congruent condition around the time of 200ms in the late blind is corroborated by comparing RoC and correlation coefficients between the four groups. Differences between the RoCs of the summed and simultaneous conditions in late-blind individuals were higher ($\Delta RoC = 0.40$) compared to sighted adults ($\Delta RoC = 0.03$), adolescents ($\Delta RoC = 0.29$), and early-blind ($\Delta RoC = 0.02$) individuals, indicating stronger activation changes in summed unimodal GFPs during this time period compared to simultaneous GFPs in the late blind. Furthermore, correlation coefficients indicated lower correlation of the GFPs in both conditions in late-blind adults (r = 0.511) compared to the other three groups (early blind: r = 0.82; sighted: r = 0.868; adolescents: r = 0.949), demonstrating less similarity between the two signals. Lastly, the second time window at 400-465ms in late-blind adults showed a moderate difference in the rate of change between the summed unimodal and bimodal GFPs ($\Delta RoC = 0.79$), and a strong negative correlation. This supports the stronger deactivation in the simultaneous GFPs compared to a stronger activation in summed unimodal GPFs within this time frame, as can be seen in Figure 8. Taken together, these measures indicate a decreased activation/deactivation to multisensory stimulation in lateblind adults during the time window of the P2, within which we found multisensory interaction effects in the sighted and early-blind adults. Furthermore, late-blind show smaller GFP in the bimodal compared to summed unimodal conditions at a later time window, coinciding with the N400, with the strongest differences expressed in right frontal regions. Grand average potentials at the midfrontal electrode cluster (see Figure 4) show that responses in bimodal conditions largely follow those of the haptic condition, suggesting sensory processing in this time window is dominated by the haptic percept.

Topographic plots of the single conditions at GFP peak latencies (202ms, 196ms, 200ms, 204ms for sighted adults, sighted adolescents, early-blind, and late-blind adults, respectively) can be seen in Figure 9. While auditory processing at this time point shows similar distribution of activation, haptic information processing shows more variability between groups. Note that the haptic potentials were smaller in amplitude and occurred relatively earlier compared to the time-locked auditory signals. Therefore, larger variability between the groups is likely due to different cognitive mechanisms in the haptic–only conditions. The distribution of summed unimodal activity is therefore more similar to that of the auditory-only condition than would be expected if auditory and haptic stimuli were exactly time-matched. Unisensory processing is more posteriorly distributed in sighted adolescents (haptic) and late-blind adults (auditory, haptic), compared to sighted adults and early-blind adults. Notably, only early-blind individuals show strong frontal inhibition during the bimodal congruent condition, while the other groups show stronger positive activation at frontal regions in the bimodal condition, compared to the summed unimodal conditions.





Figure 9: Topographical plots showing areas of high positive and negative activation at peak GFP around 200ms (see main text). Plots are shown for all conditions separately, as well as for the sum of unisensory activations and for the difference between summed unisensory and simultaneous maps. The difference maps (bottom row) indicate areas of enhancement (blue) or inhibition (red) in response to multisensory stimulation. The auditory-only and haptic-only maps are shown separately to indicate the contribution of both unimodal processing sources to the summed potential. Note that each map is scaled to the maximum absolute activation at this time point for each condition, separately.

Discussion

The present study investigated how visual experience early in life cross-modally influences the neural basis of non-visual multisensory integration. We therefore assessed differences in event-related neural processing of audio-haptic size information in sighted and non-sighted adults. We further measured event-related neural responses in a group of adolescents with typical sight, who have been shown to transition to optimal integration

over the ages of 13-17 years to disentangle the role of visual experience from maturation of multisensory processing during adolescent development.

Our results support our first prediction that reliability-weighted audio-haptic integration takes place at mid-latencies in typically sighted adults (240ms-315ms) and early-blind (200-275ms) individuals. This is reflected by modulations of the P2 component at midline frontal electrode sites. Topographical plots further suggest the involvement of the left inferior frontal regions. Notably, the inferior frontal gyrus (IFG) has been repeatedly shown to be involved in multisensory processing (Bernasconi et al., 2018; Renier et al., 2009) and is known to play a crucial role in response inhibition and top-down control (Aron, Monsell, Sahakian, & Robbins, 2004; Swick, Ashley, & Turken, 2008). Since the behavioural performance at group level shows that both sighted and early-blind individuals integrate audio-haptic information statistically optimally, the present results indicate that the ability to reduce perceptual uncertainty by optimally integrating audiohaptic information involves the contribution of higher-order processing areas and takes place at mid-latencies. Our findings thereby converge with those from previous studies assessing multisensory integration of vision and audition (Boyle et al., 2017; Cao et al., 2019; Rohe & Noppeney, 2015), suggesting that multisensory reliability weighting depends on attentional control that is reflected by neural modulations at mid-latencies in supramodal integration areas (Nikbakht, Tafreshiha, Zoccolan, & Diamond, 2018; Spagna, Mackie, & Fan, 2015). However, there are important differences between the multisensory effects in early-blind and sighted adults that are worth discussing. Firstly, multisensory integration effects in sighted adults take place at later latencies than in the early blind. Secondly, while sighted adults show a super-additive multisensory response (AH > A+H), early-blind individuals show a sub-additive response (AH < A + H). Thirdly, while the Global Field Power of audio-haptic bimodal responses was similarly strong as that of the summed unimodal responses in sighted adults, the early blind showed enhanced global activation in the summed unimodal conditions, but not in the bimodal condition throughout, similar to late-blind adults and sighted adolescents. We found that some of these differences can be explained by the activity distribution across the headspace, showing that the increase in perceptual precision through multisensory integration is achieved by different processes in the sighted and early blind. That is, the frontally distributed P2 is known to be involved in attentional modulations, which can either enhance or suppress sensory information (Crowley & Colrain, 2004; Melara, Rao,

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& Tong, 2002; Nunez, Vandekerckhove, & Srinivasan, 2017). The topographical distributions of peak activations show that, while similar regions are involved in the processing of multisensory information, they enhance multisensory information processing in sighted adults, while they inhibit sensory information processing in early-blind adults. This suggest that early-blind individuals achieve optimal (and even supra-optimal) multisensory integration performance by inhibiting the less reliable information, while sighted adults improve perceptual performance by enhancing the more reliable sensory information. This finding is supported by previous research on dark-reared cats, showing an increase in the proportion of response-inhibiting neurons that govern multisensory integration (Carriere et al., 2007). Furthermore, several studies have reported enhanced excitability of auditory processing substrates in blind individuals (Hötting et al., 2004; Röder et al., 1999), which might explain the increase in overall activation to summed auditory and haptic responses.

Another reason for assuming that the multisensory modulation we found at the P2 component reflects behaviourally-relevant multisensory integration is that this effect temporally coincides with the transition from sensory information encoding (130ms-350ms) to perceptual decision making (250-600ms; Mostert, Kok, & de Lange, 2016). While the first step is important for combining sensory information into a coherent multisensory percept, the latter step is important for forming a final percept that integrates current with previous evidence and for preparing perceptual representations for a behaviourally relevant action (e.g. task response). Finally, the finding that audio-haptic integration effects occurred at earlier latencies in the early blind compared to the sighted, might depend on sensory compensation. That is, in the single modalities, early-blind individuals typically exhibit compensation effects at the stage of early sensory processing (Hötting & Röder, 2009; Röder et al., 1999). These compensational changes might, in turn, facilitate perceptual processing at later stages, leading to a decrease in reaction times as reported by several previous studies (e.g. Barutchu, Freestone, Innes-Brown, Crewther, & Crewther, 2013; Brandwein et al., 2011; Sperdin et al., 2009). Under these circumstances it would not be surprising to find that multisensory modulations emerge at earlier latencies in early-blind compared to sighted adults. In fact, the earliest multisensory interactions were detected at 100-150ms over midparietal areas in the early blind, which might facilitate perceptual processing at later stages of processing.

Sighted adolescents, who are transitioning from sensory dominance to optimal integration show later multisensory interaction effects, largely dominated by the N2, while small but not significant differences can already be observed at earlier time windows (see Figure 6). Similarly, we recently reported that children aged 5-7years show congruency modulations of the N2 when audio-visual information was presented together with haptic information (Scheller et al., 2019), indicating that modulations of N2 may reflect mechanisms of perceptual dominance. A potential explanation for not finding a significant modulation of the P2 in our adolescent group is that participants were, on average, at the youngest age limit (13.8 years) at which we found adult-like levels of integration to emerge (13 years, see Chapter 3). As the behavioural data of the present group suggests, this group did, on average, not reach adult-like levels of audio-haptic integration. Taken together with these previous findings, our results for the adolescent group seem to reflect the transition from sensory dominance in childhood to optimal integration in adulthood.

While early studies on the development of the P2 have found that latency and amplitude characteristics of this component typically fully mature within the first 2-3 years of life, later studies extended these findings in the spatial domain by showing that the amplitude of the P2 at frontal sites increases throughout development and reaches adult-like levels only later (Oades, Dittmann-Balcar, & Zerbin, 1997; see Crowley & Colrain, 2004 for a review). The increase in amplitude of the P2 at frontal sites can also be observed when comparing our sighted adolescent and adult groups. This further supports the idea that optimal multisensory integration of touch and sound requires attentional control, reflected by an enhancement of the frontally distributed P2 component.

Furthermore, sighted adolescents showed lower global activation in the simultaneous compared to summed unimodal conditions. This might be due to increased common activations in auditory and haptic conditions that are not directly related to their sensory processing. That is, it could be related to an enhanced effort in exhibiting motor control, given that all conditions contained an element of active touch. By adding up common activations in the auditory and haptic only conditions would lead to an inflated GFP in the summed compared to the simultaneous condition (see also Stevenson et al., 2012). However, we did not compare the total power between conditions but the synchrony in global activation between conditions. In other words, we assessed whether peaks in global activation occur in both summed and simultaneous conditions at the same latencies.

Therefore, common activation does not affect the analysis conducted here. Nevertheless, it is interesting to note that additional common activation was present not only in sighted adolescents, but also in adults with early- and late-onset blindness. In the blind groups, this might indicate additional processing resources that facilitate non-visual sensory processing. As noted above, previous research found increased excitability of sensory processing substrates in the blind (Hötting et al., 2004; Röder et al., 1999), likely reflecting a compensatory adaptation to facilitate unisensory processing. It would be interesting for future studies to investigate the sources that contribute to common activation of sensory processing in the remaining senses of sensory deprived individuals and developmental populations. This would allow us to make better predictions about the perceptual and cognitive functions that might become enhanced or impaired following sensory loss during development, and therefore allow us to better gauge the potential of specific rehabilitative technologies for the sensory impaired.

Our findings further suggest that late-blind individuals, who do not integrate audio-haptic information in an optimal fashion, show altered sensory processing, both at midfrontal electrode sites as well as on the global level. GFP showed that the peak activation of the P2 was clearly present in the summed unisensory conditions, but not in the bimodal condition. Interestingly, while there was no prominent P2 of the auditory potential at frontal sites (where integration effects for the sighted were found), the haptic potential showed a delayed enhancement in response that was not present in either of the other groups. This suggests that, in contrast to our initial prediction, the absence of a multisensory integration benefit might be due to changes in both unisensory and multisensory processing.

Similar to sighted adolescents and early-blind individuals, overall GFP in late-blind individuals was lower in the bimodal condition. However, the topographical plots revealed that activity distribution was more similar to sighted adults and adolescents than to the early blind, by showing an increased frontal negativity in the summed unimodal, but not in the bimodal condition. Furthermore, topographical plots in the bimodal condition do not show an enhancement in frontal activity as we observed in the sighted adults. This suggests that the absence of the P2 in the bimodal condition is a result of the lack of sensory enhancement of the more reliable sense, and not, as in early-blind individuals, a suppression of sensory signals. This provides first evidence for the

mechanisms that lead to the impairment of late-blind individuals to integrate sensory information in an optimal fashion.

Furthermore, we found a frontal multisensory modulation in late-blind adults at 84ms-110ms, around the time of the P1, as well as global activation differences at 400-465ms. As these effects are not primary to our investigation of group differences in optimal integration, but might offer insights into the changes that lead to an impairment of optimal integration in this group, they will be discussed in further detail in the Supplementary Material S2.

We aimed to disentangle the extent to which sensory experience or perceptual maturation during adolescent development account for the processing differences in late-blind and sighted adults. We found that late-blind adults showed marked differences both in the temporal and spatial processing of multisensory information compared to all other groups. While in early-blind individuals multisensory processing was regulated by sensory inhibition, this was not the case in the late blind. In fact, late-blind adults achieved multisensory modulations by an enhancement of sensory information, similar to the two sighted groups. On the other hand, late-blind individuals differed from sighted adolescents and adults in that they showed no multisensory modulations within the time frame of the P2 nor the N2. However, similar to sighted adolescents, the late-blind showed a more posterior distribution of activation in both the summed unimodal and the bimodal conditions. Condition-specific topographical plots further indicate that the posterior shift in the summed unimodal activation of the sighted adolescents can be largely explained by haptic processing, while in late-blind adults both auditory and haptic activations contribute to this shift. Similarly, auditory ERPs at frontal electrodes showed that lateblind adults did not exhibit pronounced positive components (P1, P2), as compared to the other groups. Haptic ERPs at frontal electrode sides, on the other hand, seemed to compensate for this absence by showing an enhancement around the time of the P2. This effect was only present in this group. As these differences in unimodal processing cannot be attributed to maturational change, our findings suggest that a late loss of vision leads to reorganization of auditory and haptic processing substrates that takes place after the initiation of multisensory network maturation (Gogtay et al., 2004; Ortiz-Terán et al., 2016). Thereby, multisensory networks are established under the influence of vision and might misattribute sensory weights among the remaining modalities.

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As this is the first study to date that has examined neural processing of statistically optimal multisensory integration using sound and active touch, there are important factors that need to be considered when interpreting the results which will be discussed below. One potential limitation of studying multisensory interactions using the summed vs simultaneous comparison is the temporal onset discrepancy between haptic and auditory stimuli. However, as this discrepancy did not disrupt functional audio-haptic integration, which is the main interest of the present study, this latency shift might not be problematic. In fact, recent studies showed that stimulus-induced phase resetting of neural oscillations can have cross-modal effects that support the integration of multisensory information (Lakatos, Chen, O'Connell, Mills, & Schroeder, 2007; Mercier et al., 2013, 2015). Mercier and colleagues (2013) reported that auditory stimulation influences ongoing oscillatory phase in the visual cortex and enhances visual processing. Likewise, visual stimulation influenced the phase of ongoing oscillations in the auditory cortex, thereby enhancing auditory processing (Mercier et al., 2015). Indeed, oscillatory phase resetting has been argued to be a key component of behaviourally effective multisensory integration (Lakatos et al., 2007; Mercier et al., 2013; Senkowski, Schneider, Foxe, & Engel, 2008) as it allows for setting up the temporal structure within which sensory information can be combined. Effectively, this means for the present study that differences in temporal onset between the auditory and haptic stimulation still allow for a component-based comparison between unimodal and bimodal components (i.e. bimodal P1 appears around the same time as the auditory P1, with the exception of the late blind). However, as the auditory stimulus appears last and is adding multisensory information to the haptic tap, it is not surprising that the time course of the bimodal ERPs follows the auditory response more closely.

Another potential limitation is that no behavioural data were acquired to assess audiohaptic optimal integration during the ERP study. Our decision was based on previous multisensory ERP studies that assess multisensory interaction in children and adults without requiring a behavioural response (e.g. Brett-Green et al., 2008; Brett-Green et al., 2010; Scheller et al., 2019). Furthermore, we previously (Chapter 3) determined the ability to optimally integrate audio and haptic information in the same participants taking part in the current ERP study. We confirmed that the subsample of participants tested here are representative of the full sample tested in the previous behavioural study. Measuring optimal integration during an ERP study is not trivial, as the benefit of the multisensory condition can quickly disappear with the repetition of the limited number of stimuli (2 balls/sounds in our study). In fact, the majority of studies measuring multisensory benefit during ERP recordings used reaction time facilitation (e.g. Barutchu, Freestone, Innes-Brown, Crewther, & Crewther, 2013; Brandwein et al., 2011; Sperdin et al., 2009). Hence, we decided that a behavioural measure of optimal integration assessed before the ERP study would be more accurate and more representative of the real process. The fact that our findings are in line with studies that did and did not use behavioural measures during ERP recordings strongly suggest that the effects reported here indicate the processing of optimal multisensory integration.

A notable limitation is the small sample size of the blind adult groups. Typically, interindividual variation in ERP studies resulting from several factors such as age, bone conductance and synaptic density requires large participant groups to observe robust effects, especially when addressing differences in sensory and early perceptual processing (< 100ms). Therefore, a larger sample size of late-blind individuals would be needed to replicate these findings of an absence of multisensory modulations within the P2, before these findings can be generalized to the late-blind population. However, studies with blind individuals are often smaller in sample size due to the limited access to these populations (e.g. Cappagli, Finocchietti, Baud-Bovy, Cocchi, & Gori, 2017; Garcia, Petrini, Rubin, Da Cruz, & Nardini, 2015; Leclerc et al., 2000; Vercillo, Milne, Gori, & Goodale, 2015). Furthermore, the effects observed in our study are consistent across subjects within each patient group, with exemption of the late-latency components in the late-blind group, which likely reflect individual differences in perceptual decision making. Therefore, although we cannot currently generalize these findings to all late-blind individuals, this study provides an important contribution from which future studies can derive testable predictions about the neural mechanisms of adaptive and mal-adaptive developmental plasticity for multisensory perception processes.

Our predictions about the temporal and spatial correlates of optimal integration were based on findings from studies using audio-visual tasks (Boyle et al., 2017; Rohe & Noppeney, 2015, 2019), which suggested the involvement of higher-order processing areas and attentional processes. Given that we observe multisensory effects within the predicted times windows and cortical areas, we can be more confident in that the multisensory processing effects we observed in sighted adults relate to a modalityindependent weighting process involving a fronto-parietal network that is typically involved in top-down modulatory processes (Gazzaley & Nobre, 2012; Marek & Dosenbach, 2018).

Conclusion

Our results shed light onto the mechanisms underlying differences in optimal audiohaptic integration between sighted and non-sighted individuals. In sighted and early-blind adults we identified optimal multisensory integration via difference effects between simultaneous and summed unimodal potentials. These appeared within 200-315ms poststimulus and at frontal and centro-parietal sites, highlighting that optimal multisensory integration is achieved within the fronto-parietal control network. Sighted adolescents, who are starting to transition to optimal integration show later multisensory interactions, coinciding with the N2 which is suggestive of haptic dominance. We further show that vision loss alters audio-haptic integration depending on the age of blindness-onset. Thereby, the brains of those with early-onset blindness may retain the ability to optimally integrate audio-haptic information by switching from enhancement of the more reliable sensory information to suppression of the less reliable sensory information. Individuals who lost their sight after the age of 8 years, on the other hand, do not exhibit multisensory modulations within the same time frame. Instead, they show marked differences in the processing of auditory and haptic unimodal information, which cannot be attributed to maturational changes in sensory processing. Taken together, our findings suggest a critical period for the development of optimal multisensory integration around the age of 8-9 years, during which the available sensory input determines how the brain weighs sensory information later in life.

Chapter 4 – Conclusion

Chapter 4 built on Chapter 3 by investigating the neural mechanisms of the previously reported differences in audio-haptic integration development between sighted, early- and late-blind individuals. The findings reported here complement our understanding of how audio-haptic integration develops in the absence of visual input. They show that typically sighted adults as well as early-blind adults integrate audio-haptic information statistically optimally, but only by investigating the mechanisms of this process we uncovered that both groups reach the same level of perceptual benefit through different neural mechanisms. That is, while both groups showed a multisensory modulation of the frontally distributed P2 component, this modulation was super-additive in sighted adults, while in early-blind adults it was sub-additive. This demonstrates that in sighted adults the more reliable sensory information was enhanced, while in early-blind individuals the less reliable information was suppressed. Functionally, both processes lead to the same outcome. These results support previous findings in non-human animals that showed a shift from neural enhancement in typically sighted, to neural suppression dark-reared cats during multisensory integration (Carriere et al., 2007). However, we also observed in Chapter 3 that early-blind, specifically congenitally-blind, individuals showed a larger, albeit not significantly larger, perceptual benefit compared to sighted individuals. In this group we also observed an earlier onset of optimal integration in the youngest children tested (9 years and 12 years). This would suggest that the early-blind brain processes audio-haptic multisensory information more efficiently via inhibitory control.

We furthermore found that sighted adolescents, who are, on average, not yet integrating audio-haptic information optimally, also do not show interaction effects at the neural level that are comparable to adults. In fact, adolescents showed a modulation of the negative going N2, which in Chapter 2 we found to be linked to haptic dominance on a similar multisensory task. Hence, we would expect a transition across adolescence that is marked by a positive enhancement of multisensory potentials in the earlier mid-latency range. This would be reflected by a change from a sub-additive effect in the N2 component to a super-additive effect of the P2 component. The more posterior distribution of activity across the headspace in adolescents compared to adults suggests that this might be achieved by the maturational shift towards more frontally-controlled higher-order processing networks. By using this neural marker in a larger sample size across the

adolescent age range, future studies could investigate the developmental time point at which sensory dominance transitions to reliability-weighted integration, and whether sensory experience influences the time point of this transition.

Finally, we did not find effects of multisensory integration in the late blind that were comparable to those of sighted or early-blind adults. However, this group showed marked alterations in unisensory processing of touch and sound that could not be attributed to perceptual maturation. This suggests that compensational changes in unisensory processing (e.g. audition, touch) that take place after the age of 8-9 years might interfere with multisensory processing. This further points towards a critical period for the development of optimal multisensory integration around the age of 8-9 years, during which availability of sensory input determines how the brain weighs sensory information later in life. However, replication of these findings is needed before they can be generalized to other samples, given the small sample size of late-blind adults.

Overall, the insights into the neural basis of audio-haptic integration we gained here complement our behavioural findings well. They suggest that different mechanisms lead to similar behavioural performance and can further explain the absence of integrational benefit in late-blind individuals. They further propose that the maturation of multisensory integration is still ongoing throughout adolescence, and that changes in sensory input availability during this time can critically affect its development.

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The ability of the brain to sensibly combine redundant sensory information allows us to interact with our environment in a meaningful way. However, how does the brain develop this ability? This question was posed at the beginning of this work and has guided the investigations throughout.

Chapter 1 highlighted the important role that multisensory integration plays in our everyday life, and how we can make use of multisensory information to maximize the effectiveness of interactive technology for the purpose of sensory rehabilitation. This chapter ended with several open questions that were considered important to address in order to move the field forward, the first one being "How does sensory impairment or loss influence the development of multisensory integration and, more specifically, multisensory integration of the unaffected senses?"

Overall, the studies presented in this thesis have addressed exactly this question on different levels. Firstly, we showed that, under the influence of normal visual function, optimal multisensory integration of auditory and haptic information develops throughout adolescence, between the ages of 13-17 years (Chapter 3). Younger children exhibit sensory dominance, whereby touch dominates the final percept (Gori et al., 2008; Petrini et al., 2014). On the neural level, this is reflected by an increased sensitivity to multisensory conflict in children when touch is present, reflected in a modulation of the event-related N2 component (Chapter 2). In adults, we found that integration of auditory and haptic information resulted in an increase in perceptual precision that can be predicted by the Bayesian Ideal Observer Model. This perceptual benefit persists throughout the adult life span (Chapter 3). The mechanism leading to optimal audio-haptic integration in sighted adults is characterized by the enhancement of the more reliable sensory information through the fronto-parietal control network. This was evidenced by an increase of the frontally distributed ERP component P2 in response to multisensory stimulation compared to unisensory stimulation. Young adolescents showed stronger indications of sensory dominance, which was characterized by a modulation of the N2 component and overall less enhancement through frontally-distributed control networks (Chapter 4).

The development of optimal audio-haptic integration was not affected by a reduction in visual quality, as in the case of low vision (Chapter 3). Similarly, the complete absence of visual input early in life did not impair optimal audio-haptic integration. Interestingly, early-blind children even showed an earlier development of optimal audio-haptic integration, likely affected by the increased use of hearing and touch (Chapter 3). However, while early-blind adults integrated audio-haptic information optimally, similarly to sighted adults (Chapter 3), this was achieved through different neural mechanisms in both groups (Chapter 4). While sighted adults showed an enhancement of the P2, early-blind adults showed a suppression of the P2, suggesting that sighted adults achieve optimal weighting of sensory input via an enhancement of the more reliable information, while early-blind individuals achieved the same outcome via a suppression of the less reliable sensory input.

Surprisingly, a late loss of vision led to a strong impairment of audio-haptic integration. In fact, there was no increase in precision compared to unisensory perception in individuals that went blind after the age of 8 years (Chapter 3). This could furthermore not be explained by an increase in unisensory precision. Investigating the neural mechanisms of this process revealed that late-blind individuals showed no enhancement of the P2 in response to multisensory stimulation, as has been found in sighted adult (Chapter 4). What is more, this group exhibited changes in auditory and haptic processing that could not be attributed to perceptual maturation. Taken together, these findings suggest a critical period for the development of optimal multisensory integration around the age of 8-9 years, during which availability of sensory input determines how the brain weighs sensory information later in life. At this stage we can only speculate as to why this is the case, however it is likely that the connections between low-level and higher level processing areas that mature in early adolescence (Fair et al., 2009; Gogtay et al., 2004; Ortiz-Terán et al., 2016) are under developmental constraint. That is, if latematuring multisensory networks develop in the presence of sufficient and continuous visual input, they might lead to a prioritization of visual information over haptic and auditory information for assessing size information. Therefore, it is not only the availability of sensory experience that influences how perception develops, but, critically, the time point at which a sense is lost influences how the processes, that typically mature around this age (or before), adapt to this loss.

The investigations presented in this thesis offer a new perspective on our understanding of perceptual development. By recognizing the sensory environment of the blind (and sighted) brain, and how this environment interacts with and shapes its development, we can greatly enhance our understanding of how perception is generated. This perspective will furthermore allow us to devise rehabilitation strategies for the sensory impaired that target their needs more efficiently by building on existing capacities. Over the past decades, we have come to appreciate the incredible potential that neural plasticity bears for our brains, allowing us to adapt to many changes in our environment. However, at the same time neural plasticity allows the perceptual system only to adapt within the constraints of the sensory environment it develops in. If either of these components (the perceptual system or the sensory environment) change, perception might result impaired. This is not only indicated by our findings of an impaired integration in audio-haptic information in the late blind, but by several previous studies showing that late sensory restoration in early-blind individuals does not restore visual or multisensory functions completely (Garcia, Petrini, Rubin, Da Cruz, & Nardini, 2015; Guerreiro, Putzar, & Röder, 2016; Maurer, Lewis, & Mondloch, 2005; Merabet & Pascual-Leone, 2010). Hence, compensation can appear 'maladaptive', while it, in fact, is adaptive for the sensory environment of the developing individual.

Coming back to the application of the present findings, this should make us question the approach we are taking to sensory rehabilitation. Why would we want to restore a sense in adulthood, that has been absent since early childhood, if the brain cannot use this sensory information efficiently? Would it not be more efficient to enhance those abilities that the brain has developed? The findings presented here highlight that heightened neural plasticity during childhood and adolescence allows the perceptual processing systems of the growing individual to adapt to the sensory environment they experience at that time. Children that become blind before eight to nine years of life might benefit more from using assistive technologies that substitute their absent sense with the remaining senses, instead of restoring the lost sense. The perceptual facilitation that is inherent to optimal multisensory integration allows them to surpass ocular vision by learning about visual properties through their remaining senses. Recent advances in sensory substitution technologies for the blind have been realizing the potential of the blind brain to learn about perceptual properties that are largely visual (inferring depth from size or occlusion)
through the remaining senses (Auvray, Hanneton, & O'Regan, 2007; Proulx et al., 2015; Renier & De Volder, 2010; Richardson, Thar, Borchers, Ward, & Hamilton-Fletcher, 2019). As our findings support that early-blind children can already integrate audio-haptic information optimally by at least 9 years of age, several years before their sighted counterparts, this would suggest that multisensory integration can likely benefit perceptual learning of visual concepts through sensory substitution at an early age. Indeed, a recent study by Cappagli, Finocchietti and colleagues (2017) showed that congenitally-blind children as young as 3-4 years of age can increase spatial hearing abilities with the help of a multisensory-based sensory substitution device. The Audio Bracelet for Blind Interaction (ABBI; Finocchietti et al., 2015) is a sound-emitting bracelet that is attached to the wrist or ankle of the user and thereby substitutes visual feedback of own body movements with sound. Through the consistent coupling of auditory feedback with proprioceptive information and motor control, the developing brain can exploit the benefits of multisensory information by gaining confirmation about spatial cues across the senses. This coupling of substituted (visual-to-audio) with nonsubstituted (proprioceptive-motor) multisensory information proves useful in facilitating perceptual learning (Proulx et al., 2014; Shams & Seitz, 2008). Interestingly, the increase in spatial hearing ability reported by Cappagli et al. (2017) was only present in congenitally totally blind children, but not in children with low vision. Taken together with our results, these findings suggest that multisensory-based sensory substitution would provide the most useful tool for vision rehabilitation in early-blind children.

At the same time, advances in the development of sensory restoration techniques such as retinal or cortical implants (Lewis, Ackland, Lowery, & Rosenfeld, 2015; Roska & Sahel, 2018) or gene therapy (Bainbridge et al., 2015; Dalkara, Goureau, Marazova, & Sahel, 2016; Jain et al., 2017) provide promising solutions for late-blind individuals, whose brains have been wired to perceive information visually. However, more work needs to be done in order to make the latter more economically accessible to a wider population and decrease potential health risks. Future studies need to take the reciprocal effects of sensory deprivation and perceptual-cognitive maturation into account when devising sensory rehabilitation strategies that ought to be beneficial for the individual.

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Appendix

1. Supplementary material – Chapter 3 Late- but not early-onset blindness impairs audio-haptic multisensory integration

S1. Participants

Table S1. Participant details of typically sighted adults (left) and children (right)

Adults				Children			
Participant ID	Sex	Age	Handedness	Participant ID	Sex	Age	Handedness
a1	Female	19	right	c1	Female	7	right
a2	Female	19	right	c2	Female	8	right
a3	Female	20	right	c3	Female	8	right
a4	Female	20	right	c4	Female	8	right
a5	Female	20	left	c5	Female	8	right
a6	Male	20	right	c6	Male	8	right
a7	Male	20	right	c7	Male	8	right
a8	Male	20	left	c8	Female	9	right
a9	Female	21	right	c9	Male	9	right
a10	Female	21	right	c10	Female	10	right
a11	Male	21	right	c11	Female	10	left
a12	Male	21	right	c12	Female	10	right
a13	Female	22	left	c13	Female	10	right
a14	Female	22	right	c14	Female	10	right
a15	Female	22	right	c15	Male	10	right
a16	Male	22	right	c16	Female	11	right
a17	Female	23	right	c17	Female	11	right
a18	Male	23	right	c18	Female	11	left
a19	Female	25	right	c19	Female	11	right
a20	Female	25	right	c20	Male	11	right
a20 a21	Male	25	left	c21	Male	11	right
a22	Male	25	right	c22	Female	12	right
a22 a23	Female	25	right	c23	Female	12	right
a23	Male	26	right	c24	Female	12	right
a25	Male	26	right	c25	Female	12	right
a25 a26	Fomalo	20	right	c26	Female	12	right
a20 a27	Female	27	right	c27	Female	12	loft
a27 a28	Male	20	right	c28	Female	12	right
a20 a29	Female	32	right	c29	Male	12	right
a20	Male	32	right	c30	Male	12	right
a30 a31	Fomalo	J2 //Q	right	c31	Male	12	right
222	Fomalo	4J 50	right	c31	Fomalo	12	right
a32	Fomalo	50	right	c32	Fomalo	13	right
ass 224	Female	51	right	c34	Female	15	right
a34 225	Mala	55	right	c3E	Female	15	right
a55	Fomolo	57	right	22	Female	15	right
d30	Female	20 F0	right	C30	Female	13	ngnt
a37	Female	58	right	C37	Male	13	left
a38	Female	60	right	C38	Male	13	left
a39		61 62	right right	c39	iviale	13	right
a40	Male	62	right	c40	Female	14	right
a41	iviale	50	іеп	c41	remaie	15	ieft
a42	remale	64	right	C42	Female	15	right
a43	iviale	65	right	c43	Male	16	right
a44	Female	66	right	c44	Female	17	right
a45	remale	68	right	c45	Female	17	right
a46	Male	/0	right	c46	Male	17	right

Participant information of sighted adults and children can be seen in Table S1. One sighted adult participant presented symptoms of mild congenital Strabismus, however, both eyes were fully functioning and could be attended to one at a time. Therefore, despite a reduction of visual depth information through monocular vision, the participant's visual function was unimpaired and their data were retained in the group analysis. This is further supported by research from (Kavšek & Granrud, 2012), showing that a precise object size estimation in children and adults is not dependent on the availability of binocular cues.

S2. Methods

Stimuli and stimulus presentation

When creating the sound stimuli we chose to modulate sounds amplitude of a single recorded sound, instead of recording several different sounds, in order to control for the amount of information conveyed in each modality. In sound, duration, pitch or timbre might influence size discrimination strategy at different ages. Similarly, in the haptic modality, several cues (e.g. curvature, weight, height) can be used to infer object size. Hence, manipulating only one sound characteristic, amplitude, while providing differences in only one haptic property, object height, allowed for controlled provision of a similar amount of sensory information in the two modalities. Previous experiments have shown that differences in sound amplitude can be used more reliably than pitch differences for judging object size (Grassi, 2005; Petrini et al., 2014).

Stimulus presentation was controlled using Matlab with Palamedes toolbox (version 1.8.1, released: December 2, 2015; Prins & Kingdom, 2018) on a Retina MacBook Pro. A Psi adaptive staircase (Prins, 2013) was implemented for the whole stimulus range by setting up two interleaved staircases, one for the upper (49-57mm) and one for the lower side (41-49mm) of the stimulus range. Upper and lower staircase trials were randomly interleaved, leading to 15 comparisons of the standard stimulus with a larger ball, and 15 comparisons of the standard stimulus with a smaller ball, randomly presented within one block (condition). Each participant completed all four conditions. Synchronization of sound and touch was achieved using the Psychtoolbox PsychPortAudio command library (Brainard, 1997; Pelli, 1997).

Procedure

In all blocks, participants were instructed to attend to all the sensory information available, that is, the size they felt during the haptic-only block, the size they heard in the sound-only block, and information from both touch and hearing in the two bimodal blocks. During all patting movements, participants were not allowed to grasp or lift the ball but were instructed to keep their hands as straight and flat as possible, in order to ensure that the amount of information was limited to only one object dimension (height). At the end of each trial, they were asked to give judgements about which of the two stimuli they perceived as bigger. If unsure, they had to make a guess. The number of repetitions for each comparison stimulus depended on the participants' previous responses and was determined by their discrimination accuracy and precision.

Data analysis

The two-alternative-forced-choice paradigm described in the main paper allowed us to derive discrimination thresholds from the discrimination task (Gori et al., 2008; Petrini et al., 2014; Rohde et al., 2016). The discrimination threshold provides a measure of perceptual precision, as it indicates the smallest size difference that an individual can reliably detect. As higher perceptual precision leads to a reduction in noise, the discrimination threshold offers a means to quantify the reduction in sensory noise as a result of integration. Notably, when assessing optimal multisensory integration in a behaviourally beneficial sense, noise reduction is the most important assumption that needs to be met (Rohde et al., 2016).

Participants' responses that were collected during the experiment were pre-processed in Matlab (version: R2014b, The MathWorks, USA) and further analyzed using R (version: 3.2.1). Data were sampled using an adaptive staircase (Prins & Kingdom, 2018) as this procedure allows to reliably determine psychometric characteristics while requiring fewer trials. A Psychometric function describing the probability of a participant responding that the comparison stimulus was bigger than the standard stimulus was fitted using the Quick function, which is given as

1.1
$$\psi(x; \alpha, \beta) = 1 - 2^{-(x|\alpha)^{\beta}}$$

with x describing stimulus size, varying between the standard stimulus (49mm) and the

two most extreme sizes (57mm, 41mm), α indicating the threshold and β describing the slope of the function. Both the guess and lapse rate were fixed to $\gamma = 0.5$ and $\lambda = 0.03$, respectively. Thresholds were obtained for each of the two staircases (covering the upper and the lower part of the stimulus range). They were equivalent to the point of subjective equivalence (PSE), the stimulus intensity at which a participant cannot tell the difference between two stimuli (i.e. 50% of responses "bigger"). This point can further be used to calculate the Just Noticeable Difference (JND) for the overall psychometric functions (see Fischer & Whitney, 2014). The just noticeable difference indicates the minimum size difference that can reliably be discriminated, and can be extracted as:

1.2
$$JND_i = \frac{\bar{x}_{i2} - \bar{x}_{i1}}{2}$$

Where \bar{x}_{i1} denotes the absolute detection threshold (PSE) for the lower side of the stimulus range and \bar{x}_{i2} for the upper side for each experimental condition *i*. The two PSEs are the points at which 25% and 75% of the comparison stimuli were rated as "bigger", respectively. Both JND and PSE for each participant and condition were exported for further processing in R. Discrimination thresholds (σ) were calculated based on each individual JND as:

1.3
$$\sigma_i^2 = \frac{JND_i^2}{2}$$

Maximum Likelihood Estimation was used to calculate predicted bimodal precision according to optimal integration, as given by:

1.4
$$\sigma_{bi}^2 = \frac{\sigma_A^2 \sigma_H^2}{(\sigma_A^2 + \sigma_H^2)}$$

With σ_A^2 indicating the measured variance in the auditory performance and σ_H^2 indicating the measured variance in the haptic performance.

In order to assess the developmental trajectory of optimal multisensory integration by means of optimal sensory noise reduction, we compared the measured discrimination thresholds of children and adolescents, as well as older adults, with a group of younger adults (18-44 year old). This is because optimal multisensory integration has been commonly established in this particular demographic. In order to quantify the multisensory benefit in terms of optimal noise reduction for each age group, we computed the difference between the measured bimodal discrimination threshold and the discrimination threshold predicted by MLE ($\Delta_{measured-predicted}$) for each individual

separately. This measure provides a quantified estimation of the perceptual benefit that is gained through multisensory processes alone, as each individual's MLE prediction is calculated based on their unisensory precision for touch and hearing. It thereby takes inter-individual variation in the precision of the two sensory systems into account. The lower $\Delta_{\text{measured-predicted}}$ is for each individual, the more they benefit from noise reduction through multisensory integration. After assessing the development of multisensory benefit in the sighted population, we compared adults and children with low vision or blindness with different ages of onset to the respective age groups.

Weights attributed to the haptic cue (ω_H) were calculated from discrimination thresholds in the congruent condition via:

1.5
$$\omega_H = \frac{1/\sigma_H^2}{(1/\sigma_A^2 + 1/\sigma_H^2)}$$

Please note that when auditory and haptic cues are presented simultaneously (as in the bimodal conditions) the auditory weight can be calculated as $1 - \omega_H$.

Furthermore, shifts in PSEs were assessed for the incongruent condition in which a haptic-auditory conflict was introduced in order to assess whether biases in sensory cue selection change across development. Here, weights derived from PSEs were calculated from:

1.6
$$\omega_H = \frac{(1 - \hat{S}(\Delta)')}{2}$$

With $\hat{S}(\Delta)'$ indicating the slope of a linear regression of PSEs for all values of Δ . For more information see Supplemental Data in (Gori et al., 2008).

S3. Results – Test assumptions

Discrimination thresholds

Sighted participants: With the exception of the youngest children group for sound discrimination thresholds (p = 0.01), the thresholds from all age groups and in all conditions was normally distributed (p > .05) as assessed by a Shapiro-Wilk test. Levene's test for homogeneity of variances indicated that variances were not different across age groups (p > .05). No data points lying outside 1.5 IQR were detected, assuming no outliers. As analysis of variance is robust to violations of normality, we conducted a mixed factorial analysis of variance with the conditions as within-subjects factor and age

group as between-subjects factor.

Visually impaired participants: Due to the small sample sizes for all visually impaired adult groups (all n = 3) we used non-parametric Mann-Whitney U-tests to compare visually impaired adults with sighted adults. For comparability, we used the same test to compare low vision children with sighted children. As the blind children (n = 2) and blind adolescent groups (n = 2) were even smaller in size, we conducted single-case comparisons of these individuals with the respective age-matched sighted children and adolescent groups using a Crawford-Howell t-test for single case-control comparisons (Crawford et al., 2010).

Multisensory benefit ($\Delta_{measured-predicted}$)

Sighted participants: In order to compare between age groups, parametric test assumptions were assessed for $\Delta_{\text{measured-predicted}}$. We identified one outlier in the young adult group with a $\Delta_{\text{measured-predicted}}$ outside of 1.5 IQR from the upper quartile of the distribution, which was due to an exceptionally low threshold in the haptic condition. After removing the outlier, all other assumptions of parametric testing were met in all sighted age groups. We therefore conducted independent, Bonferroni-corrected t-tests to assess the differences in multisensory integration between young adults and other developmental age groups.

Visually impaired participants: We used non-parametric Mann-Whitney U-tests and Crawford Howell case-control comparison t-tests for comparing visually impaired with sighted age-matched groups as described above for the discrimination thresholds.

Incongruent condition

Sighted participants: Shapiro-Wilk tests indicated that, with the exception of sighted young adults (p = 0.02), the data from all age groups was normally distributed (p > .05). Levene's test for homogeneity of variances indicated that variances were not different across age groups (p > .05). We identified three outliers (>1.5 IQR) in the age groups 10-12 years, 13-17 years, and 45-70 years in the sighted sample, indicating higher thresholds than the rest of the group. However, as individual differences in the response to

incongruent stimulus pairings are meaningful in that they indicate different sensory combination strategies (i.e. integration or switching between modalities), these values were retained in the analysis.

Visually impaired participants: We used non-parametric Mann-Whitney U-tests to compare sensory weights derived from discrimination thresholds and from PSEs.

S4. Results - Individual performance and integration strategies

In order to examine how individuals combined audio and haptic cues in the bimodal condition, we plotted ratios of single-cue variances (auditory/haptic) against ratios of bimodal- to haptic-cue variances for the different age groups (see Figure S.A). The red and green line indicate predictions for either relying mostly on the worse (red) or on the best (green) sensory cue. Most individual data of adults and 13-17year olds falls below the green line, with group averages decreasing on the ordinate, indicating that they benefitted from combining sensory cues in the bimodal condition. Children in both age groups, 7-9years and 10-12years, on the other hand, show a bimodal- to haptic-variance ratio that can be approximated by using the worse sensory cue. Overall, sound cues were more reliably used in the older age groups, despite haptic information remaining the more reliable cue. This indicated an improvement in reliability and use of auditory information in the bimodal condition with age. Results for the two younger age groups and the young adults reliably replicate key findings of an earlier study using a similar paradigm (Petrini et al., 2014).



Figure S4.A. Unimodal and bimodal variance ratios of sighted individuals. Individual data (black circles) and group averages (colored circles) of variance ratios for auditory and haptic single-cues (σ_A/σ_H) and bimodal-to-haptic cues (σ_{AH}/σ_H). Error bars indicate 95% CIs. Higher ratios along the abscissa indicate lower variance for touch, meaning that touch is more reliable than hearing. Lower ratios along the y-axis indicate an improvement with both cues compared to touch alone. For comparison, model predictions are plotted based on using the single worst cue (red line), the single best cue (green line), or the integration of both cues following the Bayesian model (black line).

Single-cue variances (auditory/haptic) were further plotted against ratios of bimodal- to haptic-cue variances for the visually impaired individuals, as depicted in Figure S4.. In the group of adults that lost their sight after eight years of life (late blind), integration of audio and haptic cues did not, on average, lead to an improvement in performance. They did not benefit from having a second cue available. Contrarily, the majority of

congenitally- and early-blind individuals, who lost their vision within the first eight years of life, showed a perceptual benefit in having multiple sensory cues available by means of a decrease in discrimination threshold (higher precision) in the bimodal condition compared to the more reliable unisensory condition. This improvement was evident for both the adults and children in this group, with the exception of one child – indicated as a black triangle in Figure S4.B. This 13-year old individual showed a high reliance on touch compared to audition. During testing, we observed this individual to employ different approaches of using active touch between the bimodal and haptic condition, which was likely due to experience. That is, in the bimodal condition (which was also presented as the first block to them), they tapped the ball rapidly, similar to a button press, in order to elicit the sound, and judged object size based on sound, without paying much attention to touch. This was also verbally reported by the individual after the testing session. Contrarily, in the haptic condition, which they completed last, this individual repeatedly grasped the ball slowly, thereby gaining more information about object size from touch. This might explain why this individual did not gain much perceptual precision in the bimodal compared to the haptic only condition (see Figure S4.). Due to the limited sample size of congenitally- and early-blind children (n = 4), we decided to include this individual's responses in the analysis. However, it should be noted that this individual might have used haptic input differently across the conditions, and that performance is likely better in early-blind children than the group average suggests.



Figure S4.B. Unimodal and bimodal variance ratios of visually impaired individuals. Variance ratios for auditory and haptic single-cues (σ_A/σ_H) and bimodal-to-haptic cues (σ_{AH}/σ_H) for visually impaired adults (left) and children (right) with different levels of visual experience.

Higher ratios along the abscissa indicate lower variance for touch, meaning that touch is more reliable than hearing. Lower ratios along the y-axis indicate an improvement with both cues compared to touch alone. Squares indicate group average with error bars representing 95% CIs. Model predictions are plotted based on using the single worst cue (red line), the single best cue (green line), or the integration of both cues following the Bayesian model (black line). Black triangle in right panel marks blind adolescent individual that used active touch differently (see main text above).

S4.2. Results – Typically sighted individuals - Adolescent groups

Due to the small sample size of the older adolescent group (n = 4), both groups, the younger adolescents (13-15 years) and older adolescents (16-17years) were combined in the main analysis. However, as depicted in Figure S4.2 we can observe a clear difference in the bimodal thresholds versus predicted thresholds between the age groups of 10-12 years and 13-15 years. The younger and older adolescent groups show similar bimodal discrimination thresholds, justifying the grouping of younger and older adolescents into one group (13-17 years). To confirm the developmental effect reported in our main analysis, we carried out an additional t-test between young adults and young adolescents (13-15 year olds). This test indicated no significant difference in $\Delta_{\text{measured-predicted}}$ (t(22) = 1.63, p = .292, d_{unb} = 0.383), suggesting the developmental onset of adult-like MSI at 13-15 years of age.

Figure S4.2 shows the relationship between measured bimodal discrimination threshold and discrimination threshold predicted by MLE for typically sighted individuals, with adolescent groups split into younger (13-15 year old) and older (16-17 year old) adolescents.





Figure S4.2. Predictability of measured bimodal discrimination thresholds by MLE. Measured bimodal thresholds for all individuals in five different age groups plotted against MLE-predicted threshold. Small circles represent individual data, while large circles indicate group means. Data points falling closer to the black, diagonal line indicate observed bimodal thresholds being more similar to MLE prediction. Adolescent groups are separated into younger and older adolescents to allow a clearer observation of the developmental trend. Due to the overlap, and to aid data visualization, older and younger adults have been combined into one group.

On the individual level, the youngest age at which we found children to optimally integrate audio-haptic information was 10 years. However, the large majority of 10-12-year-old children did not integrate both cues to reduce sensory uncertainty. This also highlights the individual differences in the onset of sensory uncertainty reduction, which likely depend on factors such as early sensory experience and cognitive maturation (see Nardini, Begus, & Mareschal, 2013; Petrini et al., 2014). As most studies assessing the extent of optimal multisensory integration quantitatively focus on averaged group measures, individual differences are often ignored while they can provide useful information about potential mechanisms that lead to differences in developmental onset.

S5. Results – Sensory weights

To assess how individuals weighted sensory information, and whether cue combination strategies differed between the different developmental groups, we compared individuals' performances between the bimodal congruent and incongruent condition. This allows us to disentangle whether participants weighted haptic or auditory information more strongly in order to reduce uncertainty in the bimodal congruent condition, and whether they relied more on auditory or haptic information when the cues gave conflicting information.

S5.1. Typically sighted individuals

Mean weights derived from thresholds (see Figure S5.1, left panel) were not significantly different from 0.5 for all age groups (7-9: t(8) = 2.31, p = 0.868; 13-17: t(14) = 2.14, p = 0.326; 18-44: t(29) = 2.05, p = 0.108; 45-70: t(15) = 2.13, p = 0.586), with exception from the 10-12 year olds. The latter showed significantly higher haptic weighting during bimodal integration (t(21) = 2.08, p = 0.001). Mean weights derived from PSEs in the incongruent condition (see Figure S5.1 right panel) indicate a higher weighting of haptic information for all age groups (7-9: t(8) = 3.54, p = .008; 10-12: t(21) = 2.13 p = .045; 13-17: t(14) = 3.53, p = .003; 18-44: t(29) = 5.82, p < .001), except for the older adults (t(15) = 0.07, p = .943). This is in line with the findings from Petrini and colleagues (2014), showing no difference in sensory weighting between children and young adults.



Figure S5.1. Haptic weights in sighted individuals. Mean haptic weights for the different developmental age groups derived from discrimination thresholds in the congruent condition (left) and PSE shifts in the incongruent condition (right). Values above the dashed line at y = 0.5

indicate haptic dominance, while values below this line indicate auditory dominance. Figure shows the mean weights for each age group with error bars indicating 95% CI. * = p < .05; ** = p < .01; *** = p < .001.

S5.2. Visually impaired and blind individuals

Due to small group sizes we show the individual weights derived from thresholds in Figure S5.2, upper two panels) and derived from PSE shifts (lower two panels) for individuals with low vision and for blind individuals. Mean threshold weights were not significantly different from 0.5 in any of the groups (p > .05), indicating that neither haptic nor auditory modalities dominated significantly. However, the figures show a similar trend to sighted individuals in both low vision and blind individuals, with children and young adults weighting the haptic cue more strongly while older adults weight the auditory cue more, independently of visual experience.



Figure S5.2. Haptic weights in visually impaired individuals. Individual haptic weights for the different age and vision groups derived from discrimination thresholds in the congruent condition (upper panels) and PSE shifts in the incongruent condition (lower panels). Values above the dashed line at y = 0.5 indicate haptic dominance, while values below this line indicate auditory dominance.

S6. Results – Bimodal congruency

S6.1. Typically Sighted individuals

To assess whether differences in size discrimination thresholds for congruent and incongruent conditions differed between the age groups, we carried out a mixed factorial ANOVA, using condition as within-subjects factor and age group as between-subjects factor. This revealed a significant main effect of age (F(4,87) = 14.64, p < .001), as well as a significant interaction between age and condition (F(8,87) = 5.67, p < .001; see

Figure **S6.1**). Follow-up, Bonferroni-corrected t-tests indicated that younger adults and older adults showed significantly lower thresholds in the congruent condition, compared to the incongruent condition (18-44years: t(29) = 3.72, p = .004, $d_{unb} = 0.67$; 45-70years: t(15) = 3.67, p = .01, $d_{unb} = .895$). This was not the case for the two children groups (7-9 years: t(8) = 1.85, p = .504, $d_{unb} = 0.589$; 10-12 years: t(21) = 0.99, p = 1, $d_{unb} = 0.021$), nor for the adolescent group (t(14) = 0.07, p = 1, $d_{unb} = 0.017$). This supports the findings that adults increased perceptual precision by integrating congruent information and engaged in strategy switching more frequently in the incongruent condition. Children, on the other hand, were more likely to base their size discrimination judgement on one sense rather than combining both senses.





bar) and the bimodal incongruent (light grey bar) condition. Error bars indicate 95% CI. ** = $p \le 0.01$.

S6.2. Visually impaired and blind individuals

To assess whether differences in size discrimination thresholds for congruent and incongruent conditions differed between the different vision groups, we carried out non-parametric Mann-Whitney U-tests between in three different groups: low vision individuals, blind individuals that integrated optimally (congenitally-blind and early-blind adults and children), and blind individuals that did not integrate optimally (late-blind adults). We grouped the early and congenitally-blind individuals in order to allow us to increase power, and because congenitally- and early-blind children and adults use audio-haptic information very similarly. Please note that Figure S6.2 shows all six separate vision groups.

The tests revealed no difference between congruent and incongruent condition for the low vision group (U = 65, p = .191) nor for the late blind group (U = 3, p = .50). The early blind group showed a similar trend to sighted adults, with lower discrimination thresholds in the congruent compared to incongruent condition (U = 4, p = .014), indicating that precision was higher when individuals integrated sensory cues compared to task switching or focusing on only one sense at a time.



Figure S6.2. Effect of congruency on size discrimination performance in visually impaired individuals. Mean discrimination thresholds for the different vision groups in the bimodal

congruent (dark grey bar) and the bimodal incongruent (light grey bar) condition. Error bars indicate 95% CI.

3. Supplementary material – Chapter 4

Neural correlates of audio-haptic integration in sighted and nonsighted individuals

S1. Effects of congruency

We assessed differences in conflict processing in all participant groups by comparing ERPs between congruent and incongruent conditions. Significant differences between these two conditions indicate conflict detection. Employing the same procedures as outlined in the Data analyses section 1a, 1b, and 1c, we found a significant difference between evoked potentials in the congruent and incongruent conditions at 240-315ms (see Figure S1), coinciding with the P2 and effects of multisensory integration that are reported in the main text. Deviations were already apparent from 135ms onwards, as shown by an enhanced negative response to incongruent stimuli in the N1, however, this was not found to be significant after applying the time-stability criterion. Amplitudes were significantly higher in the congruent than incongruent condition (t(22) = 3.65, p = .001, $d_{unb}= 0.64$), indicating a response enhancement towards multisensory congruent stimuli. This suggests that sensory conflict processing takes place at similar latencies in adults as reliability-weighted integration of information.



Figure S1. Congruency effect at midfrontal electrodes in sighted adults. Left plot shows grand average ERP of the bimodal congruent (green) and bimodal incongruent (pink) conditions. Color-shaded error bars indicate one standard error of the mean. Grey shaded bar indicates time window within which the responses in both conditions differ sigificantly from each other. Topographical plot shows the difference map between congruent and incongruent conditions for the time window 240-315ms. Right graph indicates mean area amplitudes for congruent and incongruent conditions. Error bars indicate 95% CI. * = p < 0.05.

We did not find any differences of evoked potentials between congruent and incongruent conditions in either of the other groups. One likely explanation for this is that, as stimulus selection was based on the individual's discrimination threshold in the bimodal congruent condition, differences between congruent and incongruent stimuli might have been too small for the individual to tell a difference. Specifically early-blind adults, who integrate audio-haptic information statistically optimally, showed overall higher precision (i.e. lower discrimination thresholds), and had therefore the smallest differences (1-2mm on average) between the stimuli. As most previous research that assessed conflict sensitivity has used standard stimuli between which conflict can be easily detected, while we matched stimuli according to the individual's discrimination precision the effect might have been reduced. For example, in a previous study using a similar set up, we used stimuli with a difference of 16mm to create a cross-modal conflict between the senses (Scheller et al., 2019). In that study, we found conflict sensitivity in young children but not adults when multisensory information, specifically including haptic information, was

available. In the present study, the difference between stimuli is much smaller, ranging between 1mm and 5mm at most. The fact that we find congruency modulations in sighted adults but not in other groups might therefore suggest that blind adults and adolescents possess different conflict sensitivity levels, which are distinct from size discrimination precision.

S2. Further audio-haptic effects in late-blind participants

Besides the absence of a multisensory processing effect around the time of the P2, as we observed in sighted and early-blind individuals, the late-blind adults showed a frontal multisensory modulation at 84ms-110ms, around the time of the P1.Arguably, while this effect is based on only a small sample, and early effects often require a good signal-tonoise ratio, it shows high consistency across all three individuals and across trials. Interestingly, this effect was marked by an enhanced response to audio-haptic stimuli, which was absent in either the auditory or haptic only conditions. This effect, too, was likely the result of an enhancement through attentional control in frontal generators, as suggested by the topographical activity distribution within that time frame. However, in comparison to the sighted, the frontal activation showed a stronger right-lateralization. As previous research has shown that multisensory processing areas are highly affected by neural reorganization during adolescent development (Ortiz-Terán et al., 2016), this might, in fact, indicate an antedated multisensory enhancement effect. That is, multisensory enhancement might already take place at early latencies in this group, however, before the allocation of perceptual reliability weights allows for perceptual decision to be made (Boyle et al., 2017; Mostert et al., 2016). Another potential explanation for this early super-additive effect might be that suppressed auditory processing leads to a stronger dominance of the haptic information. That is, the soundinduced phase-resetting over somatosensory processing areas might have triggered a somatosensory P1 in the bimodal condition. As the onset of the haptic tap happened prior to the onset of the sound (to which ERPs were time-locked), the somatosensory P1 is not visible at 100ms post-stimulus, but might have appeared earlier. In fact, as the processing at later latencies suggests, late-blind adults showed stronger similarities between haptic and bimodal potentials compared to auditory potentials, suggesting that the haptic stimulus dominated the bimodal processing.

Additionally, in the late blind, GFP plots revealed an opposite effect between summed and simultaneous potentials between 400-465ms with a frontal distribution. Inspection of midfrontal ERPs indicated a negative going deflection within this time window that might indicate the N400 component, which has been suggested to relate to the difficulty of categorization and retrieval of stored knowledge (Kutas, Van Petten, & Kluender, 2006; Stróżak, Bird, Corby, Frishkoff, & Curran, 2016). It is thought to be more pronounced when the subject has more difficulty retrieving information and matching it with current information (Kutas et al., 2006). This might indicate that late-blind participants had more difficulties matching the perceived size of the current stimulus with the size of the previously perceived stimuli to update information on the amount of different sizes used in each block. This related to the task that participants were given. In fact, unimodal and bimodal ERPs measured at frontal and central sites during this time indicate that this effect seems to be largely driven by the auditory modality, and that processing of audiohaptic information seems to be dominating the bimodal processing. Taken together, this might indicate that a failure to integrate auditory and haptic information earlier led participants to dismiss the more difficult auditory information and base their percept on the haptic size estimate.

4. HRA Letter of ethical approval



Email: hra.approval@nhs.net

Miss Meike Scheller University of Bath 2 South, University of Bath Bath BA2 7AY <u>m.scheller@bath.ac.uk</u>

24 April 2017

Dear Miss Scheller

Letter of HRA Approval

Study title:	The Development of Multisensory Integration in Sighted and
	electroencephalography to assess how vision impacts the
	ability to combine non-visual information.
RAS project ID:	197917
REC reference:	17/LO/0058
Sponsor	University of Bath

I am pleased to confirm that <u>HRA Approval</u> has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read** Appendix B carefully, in particular the following sections:

- Participating NHS organisations in England this clarifies the types of participating
 organisations in the study and whether or not all organisations will be undertaking the same
 activities
- Confirmation of capacity and capability this confirms whether or not each type of participating
 NHS organisation in England is expected to give formal confirmation of capacity and capability.
 Where formal confirmation is not expected, the section also provides details on the time limit
 given to participating organisations to opt out of the study, or request additional time, before
 their participation is assumed.
- Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria) - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

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