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DIPLOMARBEIT /DIPLOMA THESIS

Titel der Diplomarbeit / Title of the Diploma Thesis

„Functional magnetic resonance imaging of auditory and visual processing in congenital anosmics and healthy controls“

verfasst von / submitted by

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angestrebter akademischer Grad / in partial fulfilment of the requirements for the degree of

Magistra der Pharmazie (Mag.pharm.)

Wien, 2020 / Vienna, 2020

Studienkennzahl lt. Studienblatt / degree programme code as it appears on the student record sheet:	A 449
Studienrichtung lt. Studienblatt / degree programme as it appears on the student record sheet:	Diplomstudium Pharmazie
Betreut von / Supervisor:	a.o. Univ.Prof. Mag. Dr. Walter Jäger

„Brain: Not to be confused with Brian.“

- Wikipedia

Acknowledgement

I want to thank Dr. Iris Stappen and Dr. Wolfgang Jäger for their supervision and for making this experience possible.

I further want to thank Dr. Johan Lundström, my supervisor at Karolinska Institutet, for not only accepting me in his team but also trusting me with this project and always taking the time to answer my questions. Furthermore, I want to thank Dr. Evelina Thunell, who was always there to help me. I want to thank my colleagues at Karolinska for their support and for making my time there special.

Last but not least, I want to thank my friends and family. I particularly want to thank my parents for always supporting me throughout my studies and my sister, who helped me studying but also took my mind off when I needed a break. I want to thank my friends for their love and encouragement. Special thanks go to Caitlin for proof reading my thesis and Elias for believing that I can achieve anything.

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Abstract

Numerous studies have shown crossmodal plasticity after the loss of one of the senses (i.e., the occupation of brain regions previously involved in the processing of input from a lost sensory modality by the remaining senses). While this has been intensively studied for the visual and auditory senses, little research has assessed whether crossmodal plasticity occurs for the sense of smell. As such, this study aimed to investigate the effect of congenital anosmia on brain function by assessing potential differences in brain activation between individuals with anosmia and healthy controls. Initially, suitable auditory and visual stimuli were created. In the first experiment, these stimuli were tested for their recognizability and odor association. Data from twenty-two healthy participants was evaluated to choose stimuli for the second experiment. The results showed that most objects and animals were easily identified, especially when presented visually. A total of 48 different stimuli, which either had a very high or very low odor association, were chosen. In the second experiment, functional magnetic resonance imaging (fMRI) data from 16 anosmic individuals and 16 healthy controls were acquired. During scanning, participants were presented with the visual and auditory stimuli. Their task was to identify and think of the object/animal. It was hypothesized that anosmics would have increased activation in the olfactory cortex relative to controls, and that this activation is additionally stronger for stimuli with a high odor association compared to stimuli with a low odor association. We identified activations in both auditory and visual cortices as response to the corresponding stimulation, in both anosmic and control participants. However, we did not find the hypothesized patterns we were looking for. Further research is required to determine whether crossmodal plasticity is possible for olfactory areas.

Zusammenfassung

Zahlreiche Studien haben bereits gezeigt, dass der Verlust eines Sinnes zu funktionellen wie auch strukturellen Veränderungen im Gehirn der betroffenen Person führt. Diese Veränderungen werden als ‚crossmodal plasticity' bezeichnet. Während der Großteil der Forschung jene Effekte an blinden Individuen untersuchte, konnten auch einige Studien dieses Phänomen an Tauben feststellen. Untersuchungen betreffend den Geruchssinn sind hingegen bis jetzt noch spärlich. Das Ziel dieser Studie war, herauszufinden, ob angeborene Anosmie zu funktionellen Veränderungen in den Gehirnen der Betroffenen führt, bei denen sich veränderte Aktivitätsmuster im Gehirn von anosmischen Menschen im Vergleich zu Gesunden zeigen. Hierfür wurden zuerst visuelle und auditive Stimuli vorbereitet. Im ersten Experiment wurden diese auf ihr Identifizierbarkeit und Geruchsassoziation geprüft. Daten von 22 gesunden Teilnehmern wurden evaluiert um geeignete Stimuli für das zweite Experiment auszuwählen. Die Ergebnisse dieses Experimentes zeigten, dass der Großteil der gewählten Objekte und Tiere einfach zu identifizieren war, vor allem nach visueller Präsentation. Es wurden 48 Stimuli, welche entweder durchschnittlich mit einer sehr hohen oder sehr niedrigen Geruchsassoziation verbunden wurden, ausgewählt. In einem zweiten Experiment, wurden funktionelle Magnetresonanztomographie (MRT) Scans an 16 anosmische Individuen und 16 gesunde Kontrollteilnehmer durchgeführt. Während des Experiments wurden den Versuchspersonen die zuvor ausgewählten visuellen und auditiven Stimuli präsentiert. Die Teilnehmer mussten die Objekte/Tiere identifizieren und daran denken. Das Ziel der Studie war Aktivierung in Gehirnarealen, die gewöhnlicherweise für die Verarbeitung von Gerüchen zuständig sind, zu finden. Weiters wurde vermutet, dass es einen Unterschied zwischen der Aktivierung durch Objekte mit hoher und geringer Geruchsassoziation geben könnte. Es konnten keine sinnvollen Aktivierungsmuster gefunden werden. Um eine crossmodale Plastizität in olfaktorischen

Bereichen des Gehirns komplett auszuschließen, sollten jedoch noch weitere Studien durchgeführt werden.

Introduction

Olfactory sense

While olfactory input might be less important for humans than other mammals, we are often not aware of how crucial olfaction is in our everyday life. Not only do we consciously use our sense of smell for tasks like detecting hazards in our environment, enjoying our surroundings, and gustation, but olfaction also might play a role in kin recognition and mating (Havlicek & Roberts, 2009; Horth, 2007; Jacob et al., 2002), pheromone detection (Wyart et al., 2007), mother-infant-bonding (Doucet et al., 2009), and food preferences (Mennella et al., 2001). Furthermore, it has also been associated with central nervous system physiology and longevity (Murphy, 2009; Patel & Pinto, 2014).

In the past, humans were considered to have a poor sense of smell relative to other mammals (Lundström et al., 2011). A potential explanation for this assumption is the lower number of functional olfactory receptor genes in humans versus other animals (Shepherd, 2004). For example, mice have approximately 1100 functional receptor genes (Young et al., 2002; Zhang & Firestein, 2002) whereas humans have around 400 (Glusman et al., 2001; Zozulya et al., 2001). Despite this, recent studies have shown that humans might be able to smell equally well or better than other animals in behavioral smelling tasks (Bisulco & Slotnick, 2003). Furthermore, while it was previously assumed that humans could perceive around 10.000 odors (Deibler & Delwiche, 2003), a recent study has suggested that humans may be able to discriminate between many more odors than previously thought, potentially more than a million individual odors (Bushdid et al., 2014). A further reason, which could contribute to the misconception that humans have a weak sense of smell, is that when we want to describe the perceived odor, we lack the words (Stevenson, Case, and Mahmut 2007). However, if humans are as good as other species at perceiving odors despite having less olfactory receptor

genes, what could be the reason for our good smelling abilities? One hypothesis is that humans filter less particles in their nasal passage than other animals. This could allow humans to process a similar number of odor molecules as animals, despite having fewer olfactory receptor genes (Shepherd, 2004). Another explanation might be that a large proportion of the human brain is used for the processing of smells (Shepherd, 2004).

How we smell

The process of "smelling" starts with odor molecules, so called odorants, which enter the nasal cavity. This happens via two different routes: the ortho- and retronasal route. The orthonasal route involves the sniffing of odorants by drawing in air through the nose, whereas the retronasal route has the odorants pass through the mouth to the nasal cavity via the nasopharynx (Burdach et al., 1984). The retronasal route is further used to experience the olfactory components of flavor (Frasnelli et al., 2005). Next, the odorants reach the olfactory epithelium in the posterior nasal cavity (Buettner, 2017), where they dissolve into mucus and bind to olfactory sensory neuron receptors. The neurons' axons go through the cribriform plate, form the olfactory nerve (Cranial Nerve I), and synapse in the olfactory bulb. The olfactory bulb is the first olfactory relay station and is responsible for condensing, amplifying the signal as well as basal cognitive processing (Buettner, 2017). From the olfactory bulb, olfactory information then propagates to different ipsilateral targets like the anterior olfactory nucleus, piriform cortex, olfactory tubercle, and parts of the amygdala (Shipley et al., 2003). The area that gets the largest amount of information from the olfactory bulbs is the piriform cortex in the fronto-temporal junction (Lundström et al., 2011). The piriform cortex is divided into two parts; the anterior/frontal part, which is responsible for the initial neural representation of an odor and the encoding of its molecular features (Davison & Ehlers, 2011), and the posterior/temporal part, where holistic odor object formation, hedonic quality coding, and categorization is taking place (Gottfried et al., 2006; Howard et al., 2009). Using attention (Zelano et al., 2005),

expectancy (Seubert et al., 2013; Veldhuizen & Small, 2011; Zelano et al., 2011), learning (Chapuis & Wilson, 2012), recognition (Zelano et al., 2009), memory (Zelano et al., 2009) and valence-dependent responses (Zelano et al., 2007), the perceptual quality of an odor is built in the piriform cortex. In the past it was assumed that the piriform cortex only processed unisensory olfactory stimuli; however, a recent functional magnetic resonance imaging (fMRI) study demonstrated activation in the posterior piriform cortex when participants were presented with images that had an odor association (Gottfried et al., 2004). This suggests that the piriform cortex might also process multisensory information (Porada et al., 2018). From the piriform cortex, olfactory information then projects to the entorhinal cortex, amygdala, and/or periamygdaloid cortex, where the cognitive evaluation of the olfactory input takes place (Buettner, 2017). Olfactory information is further forwarded to the hippocampus via the entorhinal cortex (Lundström et al., 2011). Notably, the hippocampus plays a significant role in the encoding, consolidation, and retrieval of memories (Insausti et al., 2002). In addition to the hippocampus, other higher-order brain areas that receive olfactory information include the orbitofrontal cortex, insula, thalamus, and hypothalamus (Buettner, 2017). Of these regions, the orbitofrontal cortex is considered to be of special significance as it is where final conscious smell perception is formed (Buettner, 2017). Furthermore, the orbitofrontal cortex integrates olfactory information with information from other sensory modalities (Gottfried & Dolan, 2003), as well as the language system (Olofsson & Gottfried, 2015). This makes the olfactory sense unique compared to other sensory modalities as olfactory information only passes through two synapses, without a relay through the thalamus, on its way to brain areas known to process emotions and memory (Buettner, 2017).

Anosmia

Anosmia refers to an inability to smell. Other forms of olfactory dysfunction, besides the complete loss of the sense of smell, include hyposmia (a reduced ability to perceive odors),

specific anosmia (an inability to smell a specific odor) and functional anosmia (a reduction of the sense of smell to a degree where it is no longer useful in everyday life; Hummel et al., 2017; Kobal et al., 2000). Notably, the terms 'anosmia' and 'functional anosmia' are often used interchangeably. Anosmics are further distinguished by the onset of their condition (e.g., people with congenital anosmia are born without the ability to smell, whereas those with acquired anosmia lost their sense of smell later in life). With regard to acquired anosmia, a decreased or lost sense of smell later in life might result from sinunasal disease, head trauma, an upper respiratory tract infection, or neurodegenerative diseases such as Alzheimer's or Parkinson's disease (Damm et al., 2004; Temmel et al., 2002). With this in mind, it is not surprising that the prevalence of olfactory deficits in the general population is high (~20%; Landis, Konnerth, and Hummel 2004; Murphy et al. 2002). Despite this, it should be noted that only a very small number, around 1%, of the anosmic population, are born without a sense of smell and only constituting a mere 1:10 000 proportion of the population (Damm et al., 2004; Frasnelli et al., 2011; Henkin & Levy, 2002; Temmel et al., 2002)

The inability to perceive odors further poses certain health risks. For instance, people with anosmia may be unable to smell hazards in their environment (e.g., rotten food, smoke, gas, etc.; Temmel et al. 2002; Reiter and Constanzo 2003; Santos et al. 2004; Croy, Nordin, and Hummel 2014). In addition to this, the loss of the sense of smell has been shown to adversely affect mental health, with as much as 40% of anosmic individuals reporting symptoms of depression and loneliness (Gopinath et al., 2011; Sivam et al., 2016). Olfactory dysfunction may also affect a person's hygiene (Croy et al., 2014; Hummel & Nordin, 2005). Specifically, an inability to sense one's own body odor could lead to exaggerated hygiene (e.g., taking multiple showers a day) and excessive use of artificial fragrances (Temmel et al., 2002). It might also negatively affect personal relationships with partners, family, and friends (Blomqvist et al., 2004; Philpott & Boak, 2014). Furthermore, the sense of smell is heavily involved in the stimulation of appetite (Boesveldt & de Graaf, 2017) and the perception of

flavor (Croy et al., 2014; Hummel & Nordin, 2005; Stevenson, 2010). Thus, anosmics, with their inability to smell, were shown to have decreased appetite and tended to enjoy food less (Boesveldt et al., 2017; Temmel et al., 2002). Despite the prevalence of anosmia and its potential health risks, olfactory testing is not included in general health exams (Boesveldt et al., 2017). In lieu of olfactory testing, doctors must rely on their patients to report any olfactory deficits. However, this is problematic as it has been shown that people have trouble recognising olfactory dysfunction. For example, in a study testing people's ability to accurately rate their smelling ability, 74.2% of participants were unable to identify their olfactory dysfunction (Adams et al., 2016). In addition, finding appropriate care and treatment for this condition proves to be difficult (Boesveldt et al., 2017).

Sensory loss

We are constantly experiencing thousands of different stimuli, which we process through distinct sensory modalities. Through multisensory integration, our brain uses information from these senses to create one unified sensory experience (Merabet & Pascual-Leone, 2010). In the past, it was assumed that the lack or loss of a sensory modality had a negative effect on developmental, cognitive, and/or behavioral outcomes (Axelrod, 1959; Myklebust & Brutten, 1953). This "deficiency theory" stems from the belief that multisensory integration required the functional use of each sense (Merabet & Pascual-Leone, 2010). However, research has shown adaptions in brain regions that are associated with the processing of the remaining senses, but has also demonstrated the functional rearrangement of brain regions involved in processing input from a lost sensory modality (Merabet & Pascual-Leone, 2010). More than this, it has been suggested that these rearrangements may lead to improved performance in behavioral tasks like auditory localization (Merabet & Pascual-Leone, 2010; Rauschecker, 1995). These findings prompted discussions about whether the absence of input

from one sensory modality may lead to improved abilities in remaining senses. Consequently, many studies have examined the effects of visual and auditory sensory loss on other sensory modalities (Reichert & Schöpf, 2018).

Adaptation to blindness

Several studies support the idea that visual input is necessary to calibrate other sensory modalities (Axelrod, 1959; Frasnelli et al., 2011; Lewald, 2002; Zwiers et al., 2001). However, research has also demonstrated that the absence of visual input enhances remaining senses (Frasnelli et al., 2011). For example, in a study by Lessard et al. (1998), early blind and sighted individuals were tested on their ability to localize auditory stimuli under monaural and binaural conditions. Results demonstrated that early blind individuals performed equally as well as their sighted controls in the binaural task and better than sighted controls in the monaural task (Lessard et al. 1998). These results were replicated in later studies (Röder et al. 1999; Simon, Divenyi, and Lotze 2002; Voss et al. 2004). These spatial abilities are even found in congenital and early-blinds, lending support to the notion that humans can develop spatial perception without previous visual experiences (Collignon et al., 2008). Research has also shown that blind individuals perform equally well or better than their sighted peers in other behavioral tasks such as tactile discrimination (Alary et al., 2008, 2009; Goldreich & Kanics, 2003; Van Boven et al., 2000), auditory pitch discrimination (Gougoux et al., 2004), spatial sound localization (Gougoux et al., 2005; Lessard et al., 1998; Röder et al., 1999; Voss et al., 2004), spatial navigation (Fortin et al., 2008), speech discrimination (Niemeyer & Starlinger, 1981), and verbal recall (Amedi et al., 2003; Röder et al., 2001).

Changes in the brains of blind individuals

Without the ability to use their visual sense, blind individuals rely mostly on their sense of touch and hearing to navigate their surroundings. Therefore, it seems obvious that parts of the brain responsible for processing these sensory modalities should undergo neurophysiological changes. Magnetoencephalography (MEG) studies have shown the reorganization and expansion of auditory cortical areas (Elbert et al., 2002) and cortical finger representations in blind Braille readers (Sterr et al., 1998a, 1998b). These functional changes appear to be responsible for related behavioral outcomes, such as efficient reading skills (Sterr et al., 1998a, 1998b) and shorter response latencies when presented with auditory stimuli (Elbert et al., 2002). Furthermore, increased hippocampal volume has been shown in a morphometric MRI study on blind people (Fortin et al., 2008). As the hippocampus is involved in spatial memory and navigation (Burgess et al., 2002), this increase in hippocampal volume could explain why blind individuals have superior spatial skills relative to sighted individuals (Fortin et al., 2008; Merabet & Pascual-Leone, 2010). In addition to non-visual brain regions, it has been postulated that functional changes might also occur in visual areas (e.g., the occipital cortex). For example, studies have indicated a thickening of the visual cortex (Bridge et al., 2009; Hasson et al., 2016; Jiang et al., 2009; Park et al., 2009) and the atrophy of grey matter (Bridge et al., 2009; Ptito et al., 2008). This is, however, only happening in congenitally blind individuals and not in late-blinds, where the visual cortex either remains the same or is even thinner than in healthy individuals (Jiang et al., 2009; Park et al., 2009; Voss & Zatorre, 2012). Furthermore, the activation of the visual cortex in early blinds has been shown during auditory (Kujala et al., 1997; Röder et al., 1999; Weeks et al., 2000), olfactory (Kupers et al., 2011) and tactile (Büchel et al., 1998; Burton et al., 2004; Gizewski et al., 2003) tasks. While these activations could have come from stimulus presentation alone, transcranial magnetic stimulation (TMS) studies, in which they disrupted the normal functioning of the occipital cortex, showed that the occipital cortex is needed for both Braille reading (Cohen et al., 1997;

Kupers et al., 2007) and verbal processing (Amedi et al., 2004) in the blind. An fMRI study similarly found that the occipital cortex is involved in sound processing for blind individuals (Frasnelli et al., 2011). Specifically, it was suggested that the dorsal occipital stream, a region connected with visuospatial processing in healthy people (Haxby et al., 1991), plays a role in auditory-spatial processing (Frasnelli et al., 2011). A positron-emission tomography (PET) study further highlighted a link between neurophysiological changes in the visual cortex and increased performance in auditory spatial tasks in blind individuals (Gougoux et al., 2005).

Adaptation to deafness

Like blind individuals, people affected by deafness rely on their remaining senses in everyday life. For example, deaf individuals communicate through sign language, which uses visuospatial information. While deafness has not been as extensively studied as blindness, research has indicated that deaf individuals perform better than hearing individuals in a myriad of tasks, such as tactile sensitivity discrimination (Levänen & Hamdorf, 2001), distinguishing emotional expressions and local facial features (Arnold & Murray, 1998; McCullough & Emmorey, 1997) as well as visual attention and processing of the peripheral visual field (Bavelier et al., 2001; Dye et al., 2007; Hong Lore & Song, 1991; Neville et al., 1983; Neville & Lawson, 1987; Proksch & Bavelier, 2002; Sladen et al., 2005; Stevens & Neville, 2006). A recent study further showed that deaf individuals reacted faster to visual events (i.e., central and peripheral targets) than hearing individuals (Bottari et al., 2010). Contrastingly, deaf people do not appear to have lower thresholds than hearing people in tasks testing for contrast sensitivity (Finney & Dobkins, 2001), motion velocity (Brozinsky & Bavelier, 2004), motion sensitivity (Bosworth & Dobkins, 1999), brightness discrimination (Bross, 1979), and temporal resolution (Nava et al., 2008; Poizner & Tallal, 1987).

Changes in the brains of deaf individuals

The above behavioral findings lead one to question whether there are underlying morphological changes in the brains of deaf individuals. So far, no big changes have been found. Looking at brain areas of the intact senses, one fMRI study showed no differences in the size or responsiveness of early visual cortical areas between deaf and healthy participants (Fine et al., 2005; Merabet & Pascual-Leone, 2010). However, higher-order visual areas have still to be looked at (Merabet & Pascual-Leone, 2010). Furthermore, studies looking at middle temporal and middle superior temporal areas, both being visual areas greatly influenced by attention (Frasnelli et al., 2011; Treue & Maunsell, 1999), found increased activation in deaf individuals (Bavelier et al., 2001; Fine et al., 2005).

Furthermore, studies examining auditory cortical areas have shown functional differences in deaf versus hearing individuals (Merabet & Pascual-Leone, 2010). For example, both a MEG (Auer et al., 2007) and an fMRI (Levänen, 1998) study detected activation in the auditory cortex in response to vibrotactile stimuli. The crossmodal activation of auditory areas has likewise been shown while deaf individuals use sign language (MacSweeney et al., 2002; Nishimura et al., 1999; Petitto et al., 2000) and in response to non-linguistic visual stimuli (Finney et al., 2001, 2003). One could argue that the activation of auditory areas by non-linguistic visual stimuli could be a by-product of the sign language experience; however, one study showed no recruitment in hearing signers, suggesting that the effect is a result of auditory deprivation (Fine et al., 2005). Other studies showed increased activity in occipital-parietal cortical areas, which are related to attention, in deaf participants (Bavelier et al., 2000, 2001; Neville & Lawson, 1987, 1987).

Adaptation to anosmia

Few studies have investigated the effects of anosmia on other sensory modalities. Of these limited studies, most have focused on evaluating the impact of anosmia on the remaining

chemical senses (i.e., the sense of taste and the trigeminal sense Reichert & Schöpf, 2018). Interestingly, these studies found that anosmic individuals had decreased gustatory function (Gagnon et al., 2014; Landis et al., 2010) and an increased threshold for detecting trigeminal stimuli (Frasnelli et al., 2010). A possible explanation for these findings may be that, due to their shared cortical processing pathways (Lundström et al., 2011), chemical senses depend on each other for proper development and function (Frasnelli et al., 2011; Reichert & Schöpf, 2018). This notion is supported by research demonstrating atrophy of the anterior insular cortex and orbitofrontal cortex in anosmic individuals (Bitter et al., 2010; Peng et al., 2013; Reichert & Schöpf, 2018; Yao et al., 2014). This is significant as the anterior insular cortex and orbitofrontal cortex are both heavily involved in gustation and the trigeminal experience (Lundström et al., 2011).

However, other studies examining the effects of anosmia in brain areas responsible for non-chemical sensory modalities are yet to be conducted. Although, recent findings of activation in the piriform cortex in response to visual and auditory stimuli in normosmic individuals (Gottfried et al., 2004; Porada et al., 2018) suggests the possibility of crossmodal plasticity in olfactory cortical areas.

Changes in the brains of anosmic individuals

Research on morphological changes in the brain of those with congenital or acquired anosmia has mostly focused on the olfactory bulb, olfactory tract, and olfactory sulcus depth. This research has indicated that individuals with congenital anosmia exhibit aplastic olfactory bulbs (i.e., absent; Yousem et al., 1996) and decreased olfactory sulcus depth (Abolmaali et al., 2002; Huart et al., 2011; Peter et al., 2019), something that could not be shown in patients with acquired olfactory loss. Furthermore, it has been shown that congenital anosmics might also greatly reduced olfactory tracts (Abolmaali et al., 2002; Huart et al., 2011). However, the

olfactory bulb has been shown to decrease in volume with the duration of olfactory loss in patients with acquired anosmia (Yao et al., 2017). Besides those areas, only a few studies have looked at cortical alterations in individuals with anosmia. People with congenital anosmia show greater grey matter density in their left entorhinal and piriform cortex as well as increased cortical thickness in the medial orbitofrontal cortex (Frasnelli et al., 2013; Karstensen et al., 2018). People with acquired anosmia have also shown grey matter atrophy in olfactory-related areas, like the piriform cortex (Bitter et al., 2010; Peng et al., 2013; Yao et al., 2014, 2017). In a study testing for central processing by applying trigeminal stimuli, anosmics demonstrated decreased activation in the somatosensory cortex and cerebellum, and increased activation in the parahippocampal gyrus, cingulate gyrus, insula, and frontal lobe (Iannilli et al., 2007, 2011).

Aim and Hypotheses

The aim of the first study was to find suitable stimuli that could be used in the second study.

In the second study, we sought to investigate if there are potential functional changes in the brains of individuals with congenital anosmia, as well as if odor association has an effect on how visual and auditory stimuli are being processed both in the brains of congenital anosmics and healthy controls.

Hypothesis 1

Anosmics will have increased activation in brain regions normally associated with olfactory processing following the presentation of visual and/or auditory stimuli, compared to controls.

Hypothesis 2

The activation of olfactory brain regions in healthy individuals will be modulated by the level of odor association (high vs. low) of visual and/or auditory stimuli.

Hypothesis 3

There will be differences in activation from low and high odor association between anosmics and healthy controls.

Method

Experiment 1

Participants

Twenty-three healthy participants (14 female, M_{age} = 28, *SD*: ± 6.89, age range: 19-48) who reported having normal hearing and normal or corrected-to-normal vision took part in Experiment 1. One person was later excluded from the analysis because she did not seem to follow the instructions given to her. Participants were recruited via the internal recruitment system within Karolinska Institutet (KI), Stockholm. The study was further advertised in two Facebook groups for the Department of Psychology and Neuroscience and students studying Psychology at KI. To participate in this study, the following inclusion criteria had to be met: age between 18 and 60 years, not pregnant, and a functional sense of vision and hearing. Participants supplied written informed consent before the commencement of the study and received one movie ticket upon study completion. The study lasted for approximately 45 minutes and was approved by the local ethics committee.

Materials / Apparatus

Stimuli

Sixty easily identifiable, everyday objects with either a very weak or very strong odor association were chosen. A sound and a picture file were created for each object, resulting in 120 stimuli. Sounds were obtained from the BBC Sounds Database (http://bbcsfx.acropolis.org.uk) and Freesound (https://freesound.org). Downloaded sounds were digitally cut to approximately three seconds in length. Clips with a brief sound were looped to ensure three seconds of sound content. Finally, sound files were edited to a mean

square equalization of -23 dB loudness (Regenbogen et al. 2016) using Adobe Audition. Pictures were taken from the Open Image Dataset v4, Imagenet, and Google Image Search. Pictures were cut square and gray scaled using Matlab.

Procedure

Participants were seated in front of the screen in a dimly lit, semi-soundproof room. To familiarize them with the task, participants completed ten practice trials (two blocks of five stimuli). The experimenter observed participants during the completion of practice trials to ensure they understood the task. Stimuli presented during practice trials were not used in the experiment.

The experiment itself consisted of twenty alternating visual and auditory blocks. A schematic diagram of the auditory and visual experiment blocks can be seen in Figures 1 and 2, respectively. In each block, participants were presented with six stimuli. Visual stimuli were presented in the center of a screen. Auditory stimuli were presented binaurally using headphones. The order of the stimuli was randomized across the participants. Half of the participants began the experiment with a visual block, the other half with an auditory block. Stimuli were presented for three seconds. Each stimulus was only presented once. Following this, participants were asked to identify the presented stimulus from four given options. The choices were designed to include a possibility that could be mistaken for the correct answer, one that was rather random, and a completely random option that should never be mistaken for the correct answer. Participants made their choice using the 1, 2, 3, and 4 keys on the keyboard. Next, participants were asked to indicate how confident they were about their choice, using a slider on a scale from 25% (random guess) to 100% (completely sure). They used the left and right arrow keys to move the slider. Finally, participants were asked about their odor association for the given object. Again, they used the left and right arrow keys to move a slider on a scale from 0 (no odor association) to 100 (strong odor association). The whole experiment was

conducted in English. Furthermore, starting at participant number ten, a vocabulary list was given to each participant before the experiment to ensure that they were familiar with all the words used in the study. Participants were also given the option to take breaks in-between blocks. Overall, the actual experiment lasted around 30 minutes. Upon completion, participants were given the opportunity to ask questions and compensated with one movie ticket.

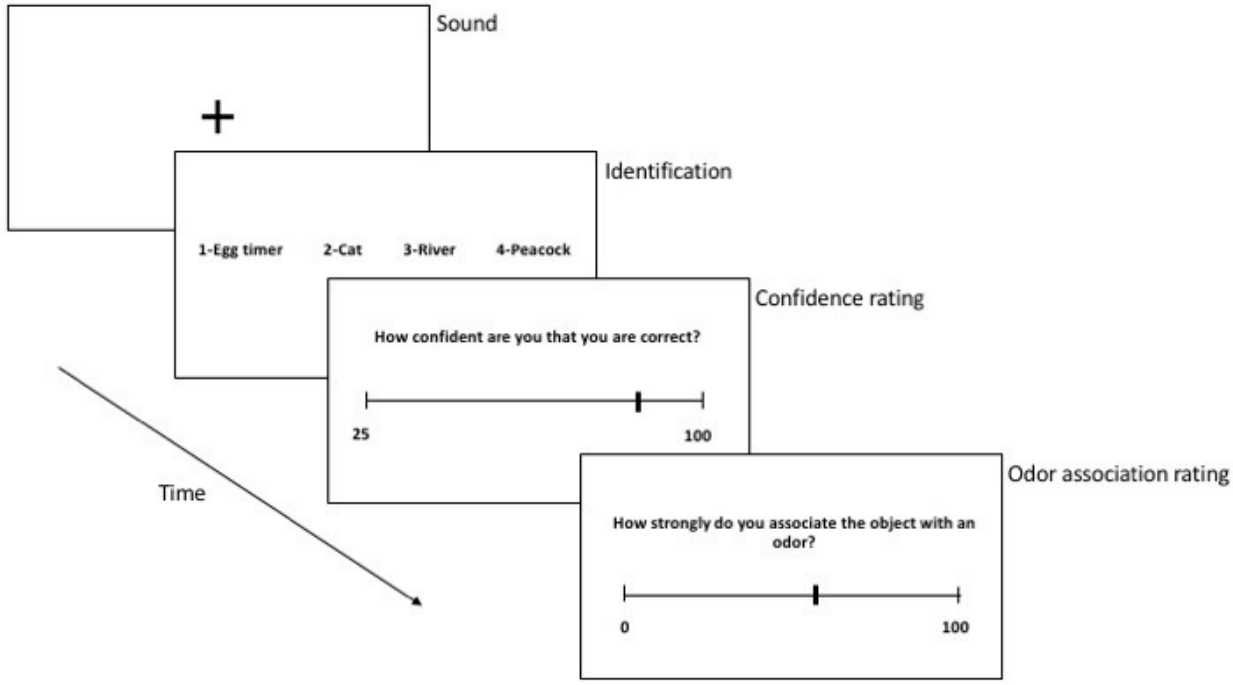

Figure 1: Sound block. The actual stimulus text was white on a grey background.

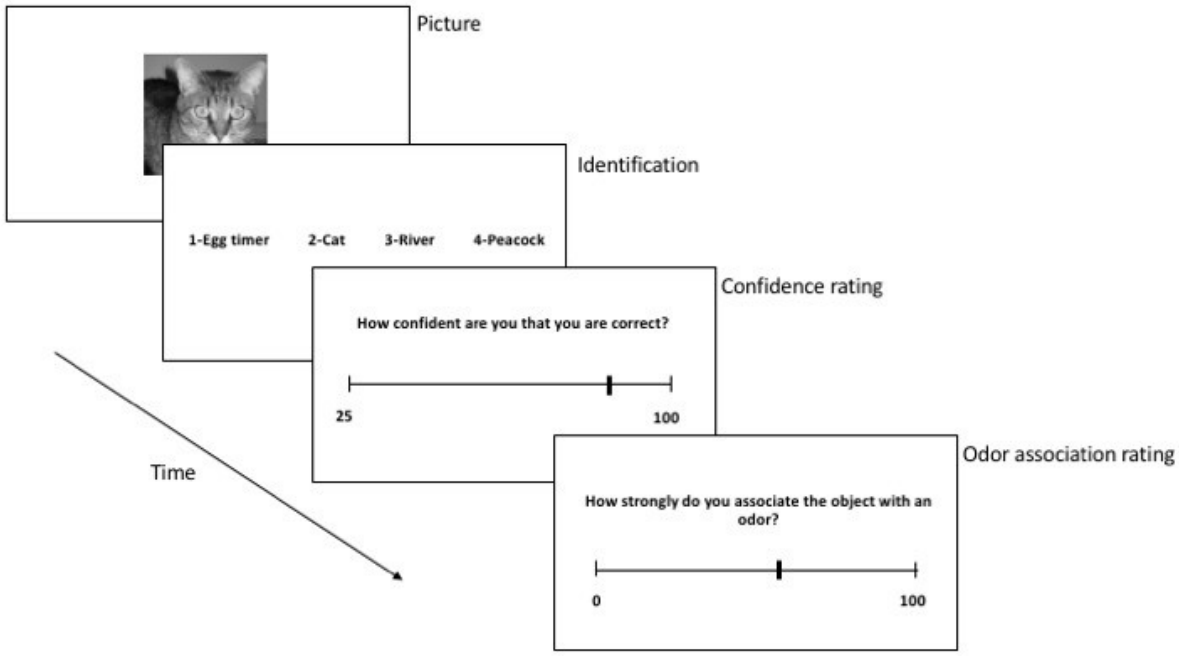

Figure 2: Image block. The actual stimulus text was white on a grey background.

Data analysis

Number of correctly identified objects, confidence ratings, odor association ratings, and response time were collated and analyzed using Matlab. Data from wrongly identified objects were excluded from analyses, since, in those cases, the participant was not rating the odor association of the actual object.

Experiment 2

Participants

Sixteen individuals with congenital anosmia and 16 age and gender-matched controls participated in the study (14 female, M_{age} = 33, SD: ± 7.88, age range: 22-49). All participants

reported having normal or corrected-to-normal visual and auditory functions. Participants further supplied written informed consent before the commencement of the study. After the completion of the experiment, participant olfactory function was assessed using Sniffin' Sticks (Kobal et al., 2000; Oleszkiewicz et al., 2019). Ethical approval was obtained from the local ethics committee.

Material / Apparatus

Stimuli

Using results from the first experiment, 48 objects/animals (see Appendix A) with either a very weak or a very strong odor association were chosen. Every object was presented as both a sound and a picture, resulting in 96 stimuli as a whole. The stimuli were divided into two groups, one containing "smelly" objects, the other "non-smelly" objects. During scanning, stimuli were additionally divided into auditory and visual stimuli. This led to four modalities, namely images with a high odor association, sounds with a high odor association, images with a low odor association, and sounds with a low odor association. These conditions make up a 2-by-2 factorial design with factors modality (visual and auditory) and odor association (low and high).

MRI

Magnetic resonance imaging (MRI) scanners, as seen in Figure 3, use three different magnetic fields to generate pictures of organs: the static magnetic field, the gradients, and the radiofrequency fields. The procedure utilizes the phenomenon of Nuclear Magnetic Resonance. That is, the ability of certain atomic nuclei to absorb and re-emit radiofrequency energy when placed in a magnetic field. Certain nuclei behave like tiny magnets – so in a magnetic field they align with it. Then the MRI scanner produces radio frequency pulse and sends it into the body to knock the nuclei out of their alignment with the magnetic field. The nuclei start to precess giving off their own radiofrequencies, which are detected by the scanner. After some time, the

signal dies off. This time is different for different tissues of the body. This is called T2 relaxation. Finally, the nuclei realign with the magnetic field. Again, the time for this to happen differs between different tissues. This is called T1 relaxation. This process is repeated over and over again.

Figure 3: MRI Scanner

Data acquisition

Scanning was performed on a 3 T Magnetom Prisma Scanner (Siemens) using a 20-channel head coil. Functional data was acquired using a 3D EP-sequence (56 slices, TR = 1700 ms, TE = 30 ms, FA = 70°, voxel size = 2.2340 x 2.2340 x 2.2000, FoV = 94 x 94) with the field of view covering the whole brain when possible. Structural images were acquired using a 3D GR/IR T1-weighted sequence (208 slices, TR = 2300ms, TE = 2.89ms, FA = 9°, voxel size = 1 x 1 x 1, FoV = 256 x 256) covering the whole brain and a 2D SE T2-weighted sequence (27 slices, TR = 4860ms, TE = 84ms, FA = 150°, voxel size = 0.9896 x 0.9896 x 2.5000, FoV = 192 x 192) covering the frontal cortex.

Chemosensory Testing

To determine each participant's olfactory abilities, "Sniffin' Sticks" were used (Kobal et al., 2000; Oleszkiewicz et al., 2019). As seen in Figure 4, Sniffin' Sticks are pen-like devices which contain odor filled cartridges and a felt tip from which the odor is perceived. In the current study, we tested odor threshold, odor discrimination, and odor identification. First, in the threshold test, participants were presented with three pens: one with an odor and two with no odor. Each pen was presented under both nostrils for 3 seconds. Participants were then instructed to identify which pen contained the odor. The discrimination test likewise involved presenting participants with three pens; albeit, in this task all three pens had an odor. Of these pens, two had the same odor while one possessed a different odor. Afterwards, participants were asked to identify which pen had the dissimilar odor. Lastly, in the identification test, participants smelled a pen containing a well-known odor. Following this, they were asked to identify the correct odor from a four-option answering card. At the end of each test a score was calculated, with a maximum of 16 points per test. For this study, the sum of the threshold, discrimination, and identification tests had to be above 30.5 for a participant to be considered normosmic and below 16 to be considered functionally anosmic.

Figure 4: Sniffin' Sticks

Procedure

The experiment was conducted by me together with another student. My task in the data collection was to operate the scanner and assist during the Sniffin' Stick testing.

Participants were welcomed and given general information about the experiment. They signed the consent form and were questioned by a researcher to check for their MR compatibility. In case they answered 'yes' to any of the questions, a MR physicist was consulted. To ensure the participants were able to identify the stimuli, training was performed. The training consisted of 4 blocks, with each block containing 12 stimuli. Along with the presentation of stimuli, the name of the presented stimulus was displayed on the screen. After completing practice trials, participants were brought to a changing room and instructed to remove any metallic objects from their person. Following this, the researcher used a metal detector to ensure participants were free of metal. Next, the researcher gave the participant detailed information about the scanning and the experiment. Before they were put in the scanner, a nasal cannula, headphones, heart rate tracker, and eye tracker were put on. In cases where the participant needed glasses, MR compatible glasses were used. After putting the participant in the scanner, the eye tracker was calibrated. Notably, eye tracking data was not analysed; instead, eye tracking was used to observe participants to ensure they remained awake for the duration of the experiment. Next, while in the scanner, participants were presented with test sounds and images to make sure that stimuli were audible and visible. Following this, participants underwent a localizer sequence. After setting the field of view, four functional runs were conducted. A run was 10.5 minutes long and comprised eight blocks. Each block lasted for one minute and contained six stimuli, which were either images with a high odor association, images with a low odor association, sounds with a high odor association, or sounds with a low odor association. Stimulus onset was random, with an average break of 10 seconds. Figure 5 shows the experiment design. After the functional scans, two anatomical scans (T1 and T2) were acquired. The field of view for T1 and T2 scans covered the whole and frontal region of the brain, respectively. Participants spent approximately 60 minutes inside the scanner. Following scanning, participants performed an odor association rating task on a computer. To familiarize them with the task, they completed a brief training session comprising one image

trial and one sound trial. During the experimental task, participants were presented with the stimuli from the scanning and asked to rate their personal odor association for each stimulus from 0 (no odor association) to 100 (very strong odor association). After the completion of the task, participants' olfactory function was assessed using Sniffin' Sticks. Overall, the experiment lasted between 2,5 and 3 hours. The experiment was conducted in Swedish. They were debriefed about the true aim of the study and were given four movie tickets as compensation.

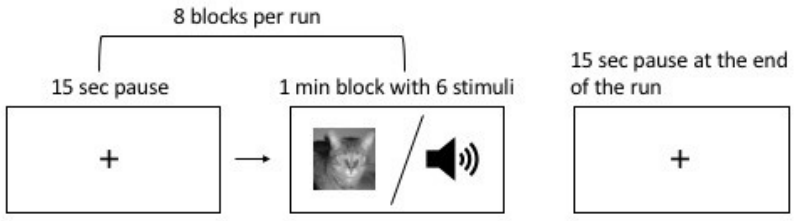

Figure 5: Experiment Design

Data analysis

The (f)MRI data were pre-processed and analysed using SPM12.

Pre-processing

Before pre-processing, all 'dicom' files were converted into 'nifti' files. Following this, slice time correction was performed. Since all slices of an image cannot be acquired at the same time, time differences in data acquisition were corrected for. In our case we also used slice acceleration during the scanning, where two slices were acquired at the same time. Next, images were realigned using estimation and reslicing. This corrects for any participant movements, by aligning each functional image to the previous one, so the voxels sample for the same location of the brain. Afterwards, during the coregistration step, a rigid-body transformation was

estimated and applied. During the coregistration the images of the different runs are all registered to a mean of the first run. This brings all images to the same position. Following this, the anatomical scans were segmented into grey matter, white matter, cerebrospinal fluid, and bone. Functional scans were normalised, using the estimate and reslice option. During the normalization, the images are deformed to match a template. This is done so data from different participants can be analysed together. In this case we used the MNI single subject template from spm12. Finally, the images were smoothed to correct for noise.

1st level analyses

In this step, we did a within-subject analysis. We had 10 regressors: 4 regressors of interest, which were our four conditions (high odor association image, low odor association image, high odor association sound, low odor association sound) and 6 additional movement regressors. For the regressors of interest we added the exact onset of the stimuli presentation. After constructing the design matrix, matrix parameters were estimated. The data from this are called beta images and tell the size of the effect the stimuli had on each voxel. Finally, for the analysis of this data, t-contrasts were used. First, we compared the effects of the two main modalities, images and sounds, hoping to find brain areas with a higher activation for one of those modalities compared to the other. For the third contrast, we checked for brain areas more responsive to stimuli with a high odor association compared to those with a low odor association. Finally, we looked into interaction effects. More specifically we investigated if the differences between the activation from low and high odor association differ between auditory and visual stimulation.

2nd level analyses

Between subject analysis was done on the second level. Using contrast images from the first level analysis, we conducted one one-sided and two two-sided t-tests. When looking for

olfactory activation and brain areas activated by “smelly” stimuli, only data from controls was used. For every analysis, we first applied FWE ($p = 0.05$). FWE stands for family wise error and revers to a 5% chance of getting any false positive result across all voxels. In case nothing survived, an exploratory analysis was conducted, lowering the threshold to $p = 0.001$ and not applying FWE.

The MNI coordinates were converted to the Talairach coordinates and using the ‘talairach client’ we received information on the exact brain areas that got the highest activation, either globally or locally.

Results

Experiment 1

Identification performance

As expected, identification was high for both visual and auditory stimuli, with a higher total number of false responses for sounds (total number: 77) than for images (total number: 15). Three sounds were excluded from analysis. “Bicycle” and “camera” were taken out due to their low sound identification performance, while the “cow” stimulus was excluded because it did not sound like a cow. The total number of false responses after exclusion were 15 for images and 56 for sounds.

No visual stimuli were wrongly identified by more than one person (see Figure 6). Contrastingly, select auditory stimuli were wrongly identified by multiple people (see Figure 7). As such, it is suggested that auditory stimuli were harder to identify than visual stimuli.

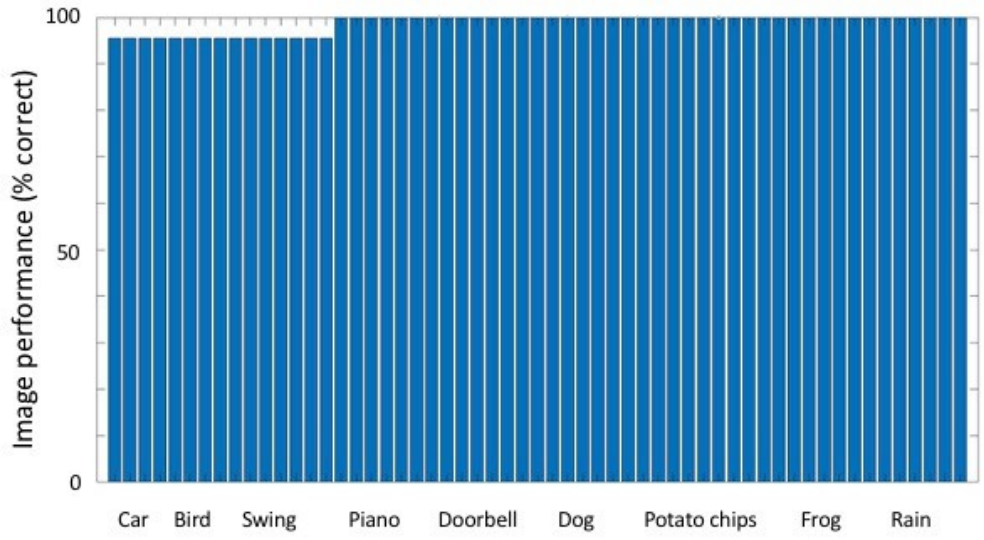

Figure 6: From 57 objects 15 were wrongly identified by one participant each (mentioned objects/animals are examples).

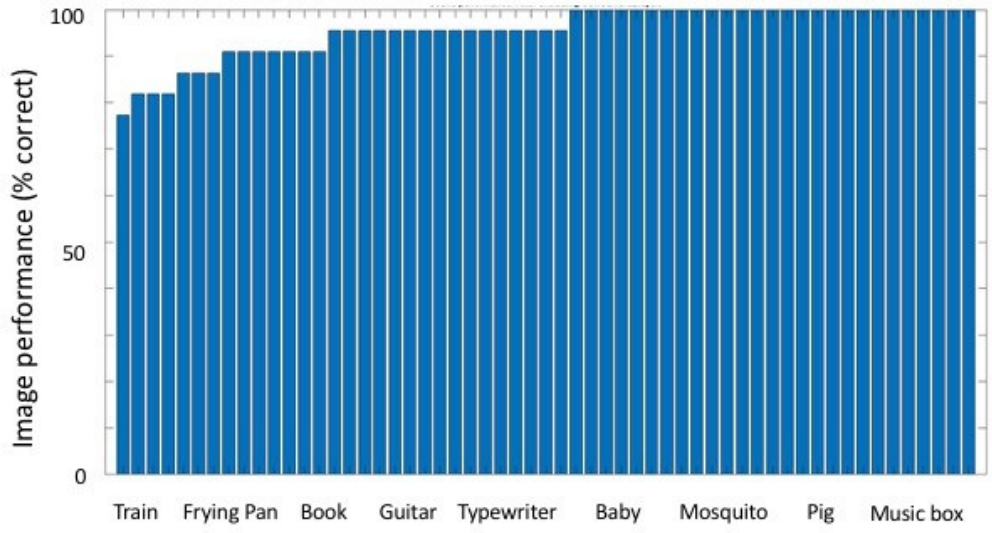

Figure 7: From 57 objects 30 were wrongly identified by at least one participant, 14 of them by more than one (mentioned objects/animals are examples).

Odor Association

A strong positive correlation between odor association ratings for images and sounds was found (r = 0.996). Figure 8 and 9 show the distribution of the odor association ratings of the 60 stimuli over 22 participants. Ratings accumulated around the lower and higher parts of the scale, indicating that most objects either had a very weak or very strong odor association.

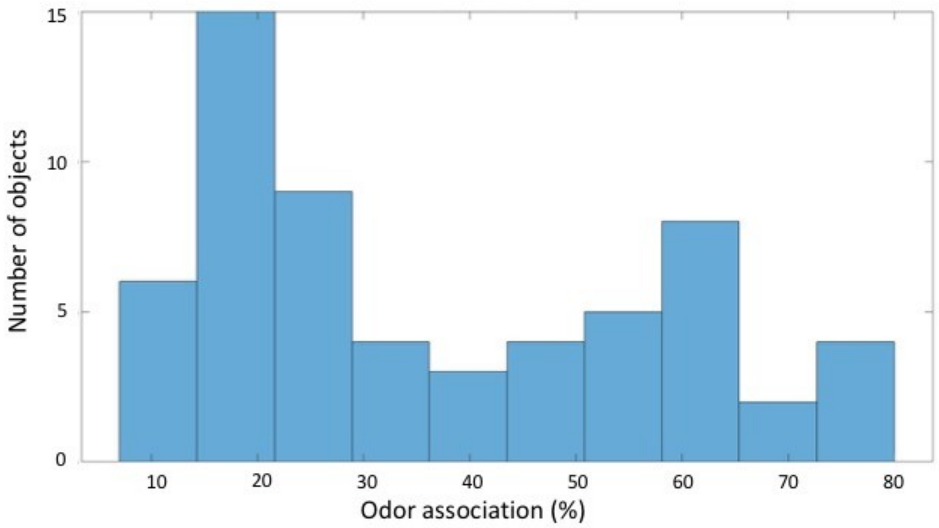

Figure 8: Distribution of odor association ratings of 60 stimuli over 22 participants.

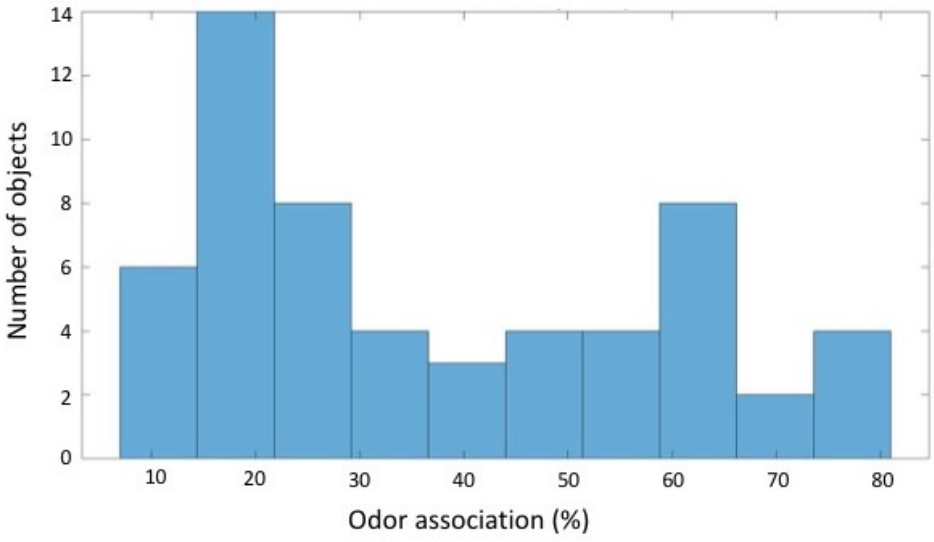

Figure 9: Distribution of odor association ratings of 57 stimuli over 22 participants.

Odor association information was used to select stimuli for the fMRI experiment. Only stimuli with a very strong or very weak odor association were selected. Figure 10 and 11 show the sorted mean odor association ratings for images and sounds, including the standard deviation. The standard deviation was large, suggesting that participants' odor associations widely varied. The two groups, stimuli with a strong odor association and stimuli with a weak odor association, should be clearly divided by a big difference in odor association ratings. As shown in Figure 10 and 11, the difference between the low odor association-group and the high odor association-group is significantly lower when only seven stimuli are excluded, compared to the exclusion of seventeen. While in Figure 10 there is almost a 30-point difference in odor association rating, it is only around 15 points in Figure 11.

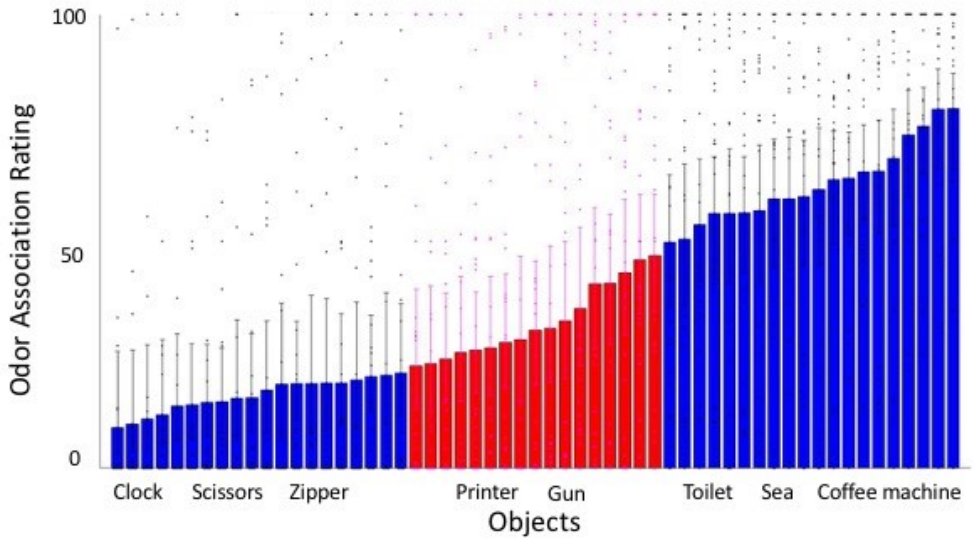

Figure 10: Odor association ratings for 57 stimuli with SD. Shown in blue are the stimuli that would be used for the fMRI experiment, those in red are the stimuli that would be excluded (mentioned objects are examples). Taking out seventeen stimuli and using the twenty lowest rated as well as the twenty highest rated stimuli results in a 30-point difference between the two odor association groups.

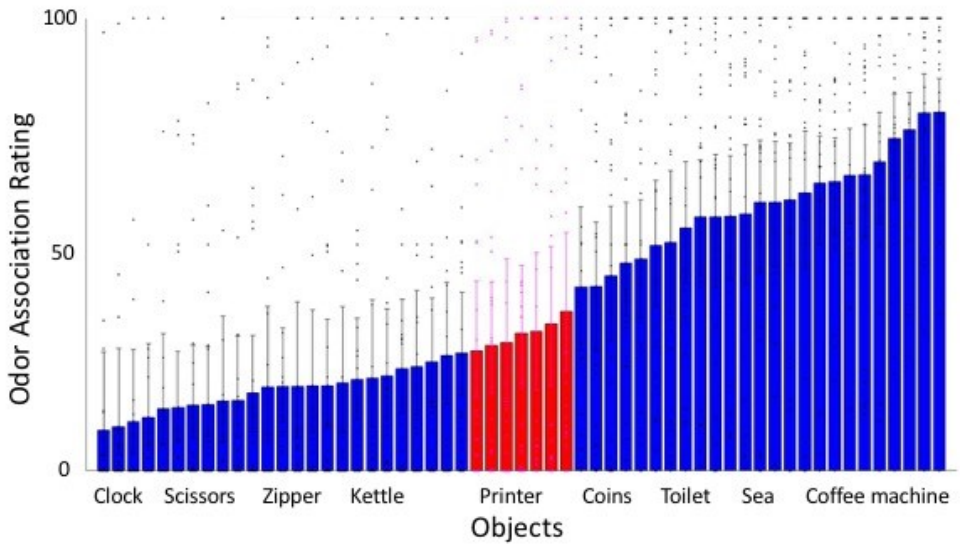

Figure 11: Odor association ratings for 57 stimuli with SD. Shown in blue are the stimuli that would be used for the fMRI experiment, those in red are the stimuli that would be excluded (mentioned objects are examples). Taking out seven stimuli and using the twenty-five lowest rated as well as the twenty-five highest rated stimuli results in a 15-point difference between the two odor association groups.

Finally, the mean odor association rating for the low odor association group and the high odor association group was determined. Figure 12 presents the difference in the mean ratings if either 40 or 50 stimuli were included in the calculations. In the end, 48 stimuli were chosen to be included in the second experiment.

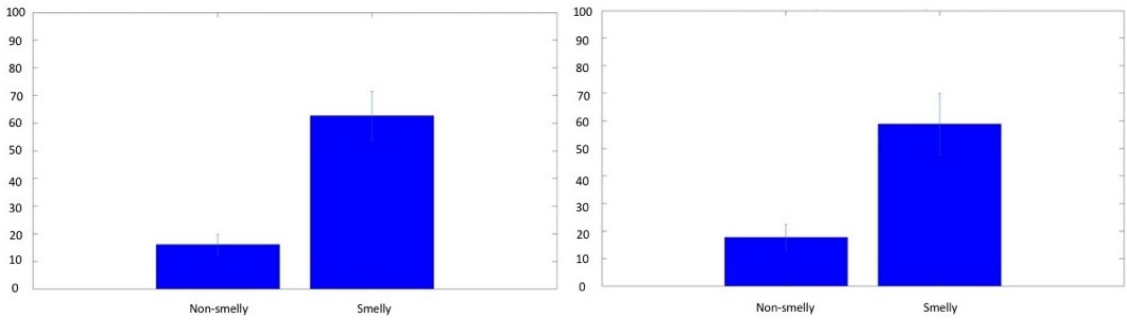

Figure 12: Comparison of the mean odor association between the two groups using 40 stimuli (left) and 50 stimuli (right). The error bars are SDs.

Experiment 2

Visual activation

First, we looked at the visual activation from the presentation of the images. As seen in Figure 13, we got activation in the visual cortices. As expected, the activation is symmetrical on both sides, since the images were presented both to the left and right of the fixation cross. High activation was found in Brodmann area 17 in the primary visual cortex (V1), 18 in the secondary visual cortex (V2) and 19 in the associative visual cortex (V3, V4, V5).

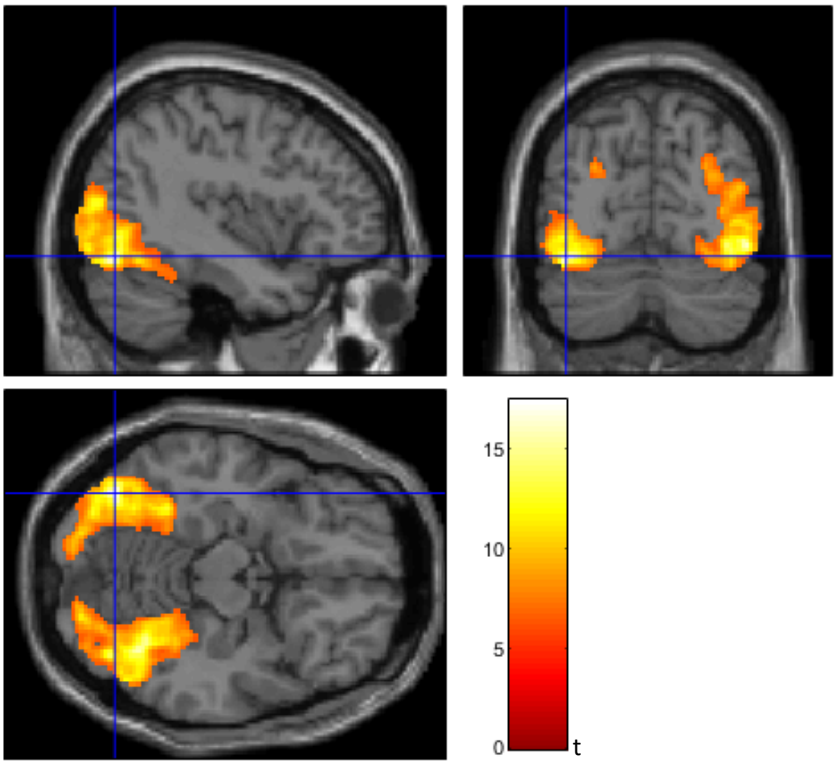

Figure 13: Activation in the visual cortex during the presentation of images: Depiction of the image>sound t-contrast displayed on the spm12 MNI single subject template on sagittal, coronal and horizontal view (MNI coordinates: x=-40, y=-72, z=-14). The colors are indicating the t-value, with a FWE correction of p<0.05.

Auditory activation

As seen in Figure 14 activation through sounds was found in the auditory cortex in the temporal lobes. Again, the activation is bilateral. The global maximum was found in an area covering Brodmann area 41 and a local maximum was found in Brodmann area 22, which are both sound processing areas.

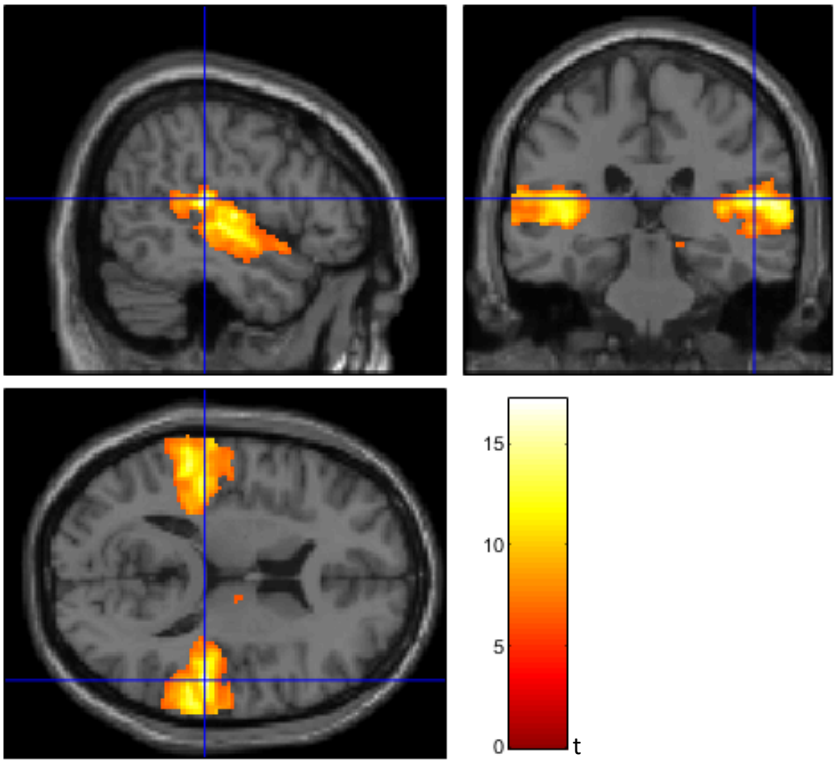

Figure 14: Activation in the auditory cortex during the presentation of sounds: Depiction of the sound>image t-contrast displayed on the spm12 MNI single subject template on sagittal, coronal and horizontal view (MNI coordinates: x=52, y=-28, z=14). The colors are indicating the t-value, with a FWE correction of p<0.05.

Olfactory activation

Looking at the activation in healthy controls in response to the objects, independent of modality, that covary with the odor ratings, no voxels survived Family Wise (FWE) whole brain error correction. When lowering the threshold to a more liberal value of $p<0.001$, some activation was found; however, the pattern, as seen in Figure 15, seems rather random and there are no activations in a priori hypothesized areas.

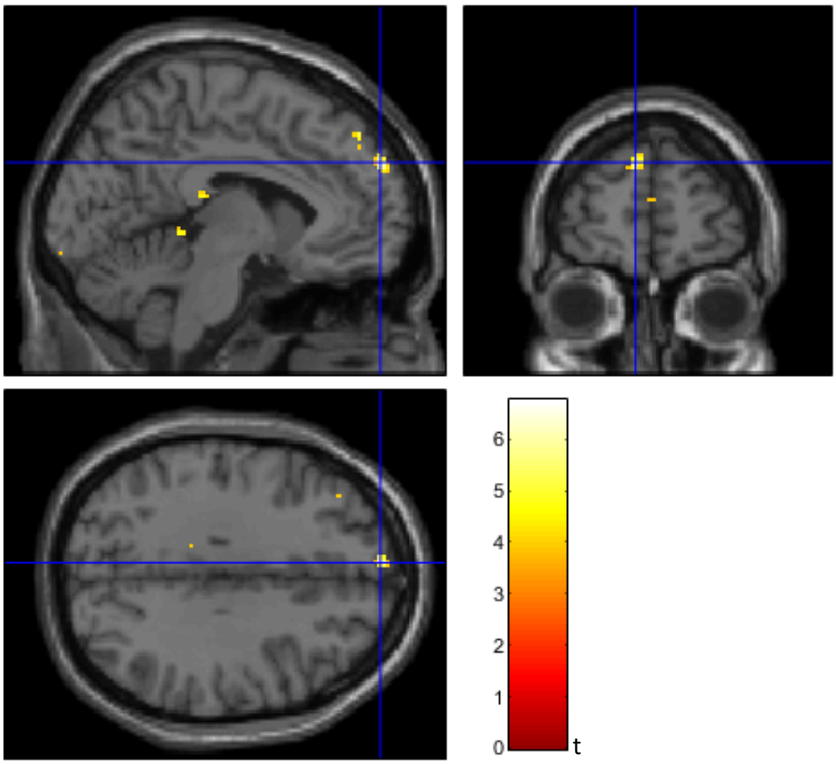

Figure 15: Activation in the olfactory cortex during the presentation of images and sounds with a high odor association: Depiction of the high odor association>low odor association t-contrast displayed on the spm12 MNI single subject template on sagittal, coronal and horizontal view (MNI coordinates: x=-6, y=58, z=32). The colors are indicating the t-value, with a statistical correction of p<0.001.

Looking for a different activation pattern through the presentation of visual and auditory stimuli in anosmics compared to healthy controls, again, nothing survived FWE correction.

Using a lowered threshold to $p<0.001$, some activation was found, but without any meaningful pattern.

Applying the FWE, nothing survived when looking at brain areas in controls only activated by objects with a high odor association. Furthermore, using an exploratory analysis, no pattern was found.

When looking for differences in the previously described interaction effects between anosmics and healthy controls, no effect was found. Whether by applying FWE or doing an exploratory analysis.

Discussion

Experiment 1

The aim of this first experiment was to find suitable stimuli to be used for the second experiment. The stimuli should be recognizable as well as having either a very high or very low odor association. The whole experiment was conducted in English, which led to participants reporting that they were unfamiliar with some of the words in the experiment and therefore have possibly given wrong answers. To avoid this, we handed out a vocabulary list and gave them the chance to ask the meaning of words beforehand. General identification was very high, probably due to the fact that we only used everyday objects as stimuli and tried to make the task fairly easy. As it was to be expected, participants performed better at identifying pictures than sounds. The reason for that could be that humans rely more on their vision than on their auditory sense and are generally better at identifying visual stimuli. We suspect that image identification mistakes were due to lack of concentration rather than inability to identify the stimulus. That suspicion is strengthened by the information we got from participants after completion of the study, when they informed us about accidental mistakes. Odor association ratings cumulated around the upper and lower end of the scale, as we had hoped for. This gave us the chance to sort out stimuli with neither a high nor a low odor association. While our goal was to have a big difference in odor association ratings between the “smelly” and “non-smelly” stimuli groups, we decided on the 24 highest and lowest scoring stimuli in order to have a large number of stimuli.

Experiment 2

This MRI study had three aims. First, to look for differences in the processing of visual and auditory stimuli in anosmics compared to healthy controls. Second, this study aimed to investigate if stimuli with a high odor association could activate olfactory brain areas in healthy controls. Finally, we wanted to see if possible interaction effects differ between anosmics and controls.

We started the analysis by looking for activation in visual, auditory and olfactory regions. We found strong activation in the visual cortex when participants were presented images. High activation was found in Brodmann area 17, which is located in V1, an area known to be strongly activated by visual stimuli. Auditory activation from sounds was, as expected, weaker than visual but still strong. In this case we found high activation in Brodmann area 41, a typical auditory brain area. No activation in olfactory brain areas was found when comparing high to low odor association stimuli in both modalities, even after lowering the p-value threshold to p=0.001. However, this was not completely unexpected considering the fact that olfactory stimulation was only indirect through the participants personal odor association and not direct through the application of an odor. Furthermore, it has to be considered that the brain areas responsible for olfaction are rather small compared to those used for visual and auditory processing. Besides, possible effects in olfactory brain areas might still be visible with a bigger sample size.

While many studies have shown adaptations in the brains of blind and deaf people, there haven't been a lot of studies examining changes in the brains of individuals with anosmia (Reichert & Schöpf, 2018). Furthermore, those that looked into changes in anosmic individuals' brains focused on the olfactory bulbs and the olfactory tract (Reichert & Schöpf, 2018). Doing a whole brain analysis, we were hoping to find a different activation pattern in anosmics compared to controls. No results were found so far, whether using a conservative FWE approach or an exploratory analysis.

Furthermore, we were hoping to find activation in olfactory brain regions after presenting healthy controls with stimuli that have a high odor association. One fMRI study already showed activation in the posterior piriform cortex after presenting participants with images (Gottfried et al., 2004). However, we did not find any signs of activity during the presentation of the stimuli. One reason for the differences in these findings could be the differences in the design of the studies. While in our study we used images of objects that were associated with odors, in the previous study only images without an odor association were used. Instead participants received olfactory stimulation together with the images and were told to form stories between each stimuli pair. Following this, they performed a recognition memory task, where they were presented with images from the previous phase and new pictures. The researches were looking for activation in olfactory areas during successful object recognition.

Finally, we were looking for interaction effects, expecting them to be bigger in controls than in anosmics. Like for the two previous hypothesis, we did not get any results. One explanation for not finding any significant results could be that the sample size may not have been big enough. Therefore, we might not have had enough power (Button et al., 2013) and smaller effects could have been overlooked.

Subject fatigue could be another reason for not getting the expected results. To avoid this problem, the Sniffin Stick test was performed at the end of the experiment. Additionally, we started the scanning with the functional scans, moving the anatomicals to the end of the scanning. When possible, we scheduled the experiments during the late morning or early afternoon. Despite those precautions, many people were extremely sleepy during the experiment, up to the point they could barely stay awake. Some even fell asleep during the experiment. Thanks to the use of the eye tracker, we could monitor their level of attendance and sleepiness and could intervene in cases where they seemed to miss stimuli. In those case we spoke to them, to wake them up again and noted this in the protocol. Reasons for the extreme tiredness could be the long runs, going for over 10 minutes, during which the participants had

to lie still. Another factor could be the simplicity of the task, which was only to focus on the presented stimuli and identify them. So, to avoid this problem, future studies could have shorter runs and might include some additional task, to keep the participant awake.

Another problem we faced was that for some subjects the field of view was not big enough to fit the entire brain. In those cases, we set the field of view to leave out the top of the head, since we were especially interested in the piriform cortex. Therefore, possible effects in those areas might have been overlooked.

Furthermore, for this study we only divided the stimuli into two groups (smelly, non-smelly), leaving out personal odor association rating. The reason for this was to simplify the analysis. However, as seen in the first experiment, every person has very different odor associations for different objects/animals. This could lead to smaller effects, due to some participants not having an association for some of the included stimuli. This thesis is based on an ongoing study which will hopefully provide more insight into this topic. The final study will therefore use the individual odor association ratings of the participants.

In conclusion, finding activation in the visual and auditory cortex through stimuli presentation showed us, that both the study design and analysis was working as intended. Unfortunately, we could not find activation in the olfactory cortex, possibly because the activation was indirect and the sample size might have been too small. None of our three hypotheses showed any results, however, this does not necessarily mean that there are no effects. More research needs to be done, which will hopefully give more insight into the effects of congenital anosmia on the brain.

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