Hemispheric Specialization of Face Processing and Spatial Cognition in Situs Inversus

Masterproef II neergelegd tot het behalen van de graad van Master of Science in de Psychologie, afstudeerrichting Theoretische en Experimentele Psychologie

Promotor: Prof. Dr. Guy Vingerhoets
Copromotor:
Begeleider:

01002907
Charlotte Boeykens
PREFACE

This Master’s thesis is the product of the contribution I have made to a larger and outmost interesting research project examining brain lateralization in individuals with Situs Inversus. I am very grateful to have been able to be a part of and delve into this particular topic that highly piques my interest. Therefore, I would like to thank my promoter, Prof. Dr. Guy Vingerhoets, for providing me this opportunity and the resources related to this research project.

Several people were essential in bringing about this research project. I would like to thank MRI research assistant Stephanie Bogaert for conducting all imaging, the university hospital UZ Gent, other students working on this project, and all participants for their contribution.

I would like to parallel my experience writing this thesis to the tale of the old man and the sea by Ernest Hemingway - If you are willing to romanticize academia, you may consider this thesis the fish, and I the old man. The fish may have been a pain to catch. Nevertheless, the fish was noble and the old man considered the fish his brother.

Due to my education at Universiteit Gent, I have experienced and learned a great amount. This would not have been possible without my parents, who have supported me out-and-out. I would like to thank my family, friends in Bornem, friends in Gent, and friends in England for all the support and great memories.

Gent, August 2016.
ABSTRACT

A vast amount of neuropsychological and neuroimaging research indicates that the left and right hemisphere in the brain each have their own specialization. Face processing and spatial cognition are typically right hemispheric dominant cognitive functions. Several ontogenetic and phylogenetic factors, amongst which anatomical differences, may contribute to the lateralization of cognitive functions. Research on subjects with Situs Inversus (SI), a condition in which visceral organs are mirrored compared to their normal position, allows us to explore the link between an innate inverted structural position of visceral organs, a possible inverted structural position of the brain, and functional lateralization in the brain. Previous research concerning SI was restricted by limited sample size, limited scope of considered functional networks, and absence of adequate control groups. The current study researched the fundamental mechanisms underlying hemispheric specialization to a greater extent by means of comparing the Lateralization Index (LI) in regions of interest (ROI) for face processing (by means of the Dynamic Face Localizer task) and spatial cognition (by means of the Landmark task) in individuals with SI to the LI in ROIs in matched controls in an fMRI setup. Results suggest that hemispheric specialization of face processing and spatial cognition does not develop independently from structural asymmetries. Nevertheless, structural asymmetries do not seem to ultimately determine functional hemispheric dominance in all cases. There are large interindividual differences concerning to which extent certain factors regulate the direction of hemispheric specialization, but structural asymmetries provide a great predictive value for functional asymmetries in most individuals.
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INTRODUCTION

Contrary to what is commonly assumed, brain regions and hemispheres do not operate as individual independent modules each responsible for different functions. Cognitive functions usually depend upon more broadly distributed neural networks (Steeves et al., 2006; Sugiura et al., 2006; Richards, & Chiarello, 1997; Flöel, Buyx, Breitenstein, Lohmann, & Knecht, 2005). Nevertheless, each brain region has its specialization and some functions are lateralized more to the right or left hemisphere. The asymmetrical representation of language, praxis, spatial cognition and face processing in the brain are robust findings in neuroscience. Neuropsychological and neuroimaging research indicate that in most people, networks of spatial cognition and face recognition have their functional centre in the right hemisphere (Leehey, Carey, Diamond, & Cahn, 1978; Kanwisher, McDermott, & Chun, 1997; Barton, Press, Keenan, O’Connor, 2002; Weintraub, & Mesulam, 1987; Harvey, Milner, & Roberts, 1995; Mesulam, 1999), whereas networks of language processing and praxis have their functional centre in the left hemisphere (Vingerhoets et al., 2012; Frost et al., 1999; Vigneau et al., 2006). Specific tasks involving these functions are robustly associated with activation of certain lateralized regions and deficits related to these functions are often due to lesions in these lateralized regions. Therefore, spatial attention, face processing, language processing and praxis provide useful tools to study hemispheric lateralization of cognitive functions. Flöel et al. (2005) stated “Lateralization of brain functions is of clinical significance, because differences in the side and the extent of attentional lateralization determine the susceptibility to attentional deficits after unihemispheric lesion”. Uncovering the origin of lateralization is of great importance, since it allows for a more in depth understanding and prediction of functional deficits. Nevertheless, an account for the causes of hemispherical specialization is yet to be provided. Contrary to functions such as motor control of limbs and sensory processing of visual input, these cognitive functions do not lateralize in a manner that is predictable or perhaps caused by bodily positions. Neither are these functions represented evenly in each hemisphere and only differing in which side they serve. Is hemispheric specialization of cognitive functions then a matter that is independent of anatomy, or are the two functions linked because of less evidently logical reasons? This thesis will mainly focus on the functional network of face processing and spatial cognition, which
are dominantly right hemispheric in normal individuals. A complementary thesis of another student will focus on the functional network of language and praxis, which are dominantly left hemispheric in normal individuals.

Although seemingly symmetrical at first sight, the brain is lateralized in its anatomy. Firstly, there is a difference in hemispheric extents, a phenomenon also known as the petalia. The surface of the right frontal lobe and the surface of the left occipital lobe protrude further than the surfaces of these lobes in the opposite hemispheres in the majority of individuals (Kennedy et al., 1999; Ihara et al., 2010). The anterior petalia range further in the right hemisphere and the posterior petalia range further in the left hemisphere. Another often described asymmetry in brain anatomy is found in the planum temporale, being larger in the left hemisphere compared to the right hemisphere (Kennedy et al., 1999; Ihara et al., 2010). The planum temporale is the posterior portion of the temporal cortex, forming the heart of Wernicke’s speech region. The structural asymmetries of the petalia and planum temporale were confirmed by Good et al. (2001), who used voxel-based morphometry in 465 normal adults and found significant asymmetry of cerebral grey and white matter in the occipital, frontal and temporal lobes.

In the following sections, spatial cognition and face processing will be discussed. Both functions are robustly found to typically have a right hemispheric dominance. Both lesion studies and research on healthy individuals will be reviewed to identify specific regions of interest associated to these typically right hemispheric specialized functions. As previous research has mainly focused on left hemispheric specialization, it may prove interesting to examine the characteristics and origins of the lateralization of spatial cognition and face processing, in order to uncover more about hemispheric specialization and structure-function relationships in general.

**Spatial Cognition**

Unilateral neglect is a neuropsychological condition in which attention and awareness of one side of space are disturbed. The deficit can establish itself after sustained damage to one hemisphere, and can therefore provide insight into lateralized cognitive functions. The anatomy of unilateral neglect after right hemisphere stroke lesions was examined by Vallar and Perani (1986). They found that neglect is more
often associated with parietal lesions, especially in the inferior parietal lobule, than with frontal lesions. Lesions confined to deep structures, more specifically the grey nuclei, can result in neglect as well. Weintraub and Mesulam (1987) concluded that there is a right cerebral dominance in spatial attention since both contralateral and ipsilateral neglect are only present in, or are more severe in patients with right hemisphere injury. In a later article, Mesulam (1999) stated that the right hemisphere specializes more in spatial attention than the left hemisphere does, with even distribution of spatial attention in the right hemisphere and a shift of spatial attention to the contralateral hemispace in the left hemisphere. Consequently, usually only right hemispheric lesions result in unilateral neglect, since these would result in a more lateralized disruption of spatial attention. Hillis et al. (2005) noted that there is a debate concerning the site of the lesion responsible for hemispatial neglect. They studied patients with right subcortical infarcts, but without any cortical lesions. The results indicated that different forms of neglect are associated with different sites of cortical hypoperfusion, as measured by magnetic resonance diffusion- and perfusion-weighted imaging. More specifically, left “allocentric” neglect was mostly associated with hypoperfusion of right superior temporal gyrus, left “egocentric” neglect was mostly associated with hypoperfusion of right angular gyrus and patients without cortical hypoperfusion showed no hemispatial neglect. Therefore, spatial cognition is influenced by more than what can be structurally detected in the brain. It may prove interesting to further specify the presence or absence of the limits of structure-function relationships, as will be discussed later on. Corbetta, Kincade, Lewis, Snyder, and Sapir (2005) provided new insights into a potential neural basis of spatial neglect and its recovery. They showed that spatial attention deficits in neglect after right frontal damage are associated with abnormal activation of structurally intact parietal regions that are known to mediate attentional processes. Recovery of spatial attention deficits are associated with the rebalancing of activity within these regions. Corbetta et al. (2005) concluded that behavioural deficits depend on both structural anatomy and physiological functional processes, indicating once more that further defining how these structure-function relationships interact would be most informative.

Several authors employed functional magnetic resonance imaging (fMRI) to research neural processes during tasks requiring spatial attention in normal subjects.
Consistent with results of lesion studies, Fink et al. (2000) observed a right hemispheric dominance in the inferior parietal lobe during the Landmark task. Additionally, right superior parietal lobe, vermis, and left cerebellar hemisphere were implicated in normal subjects. In a later study, they confirmed the right hemispheric dominance in posterior parietal cortex during the Landmark task and provided evidence for this activation irrespective of whether the stimulus had a horizontal or vertical orientation (Fink, Marshall, Weiss, & Zilles, 2001). Jansen et al. (2004) combined evidence from functional transcranial Doppler imaging (fTCD) and fMRI. They found that the Landmark task activates a large neural network, with its main activation centres in anterior cingulate cortex, lateral parietal cortex, and fronto-temporal cortex. There is right hemispheric dominance for spatial attention for most of the subjects as measured by both imaging methods. Flöel, Buix, Breitenstein, Lohmann, and Knecht (2005) confirmed that spatial attention is lateralized more right hemisphere dominant in most normal subjects, but stipulated that there is evidence for lateralization of spatial attention to the left hemisphere in some normal subjects as well. Lateralization of spatial attention is best described by signal intensity changes in those voxels in frontal and parietal regions of interest (ROI) which exceed a predefined activation level, as concluded by Jansen et al. (2006). Çiçek, Deouell and Knight (2009) also highlighted the importance of a fronto-parietal network in spatial attention allocation and found that predominantly right hemispheric lateralized processes are engaged during the Landmark task. A link between the anatomical basis of a right hemispheric fronto-parietal network and the performance of subjects in visuospatial tasks was provided by De Schotten et al. (2011). They stated that there is a significant correlation between the degree of anatomical lateralization and asymmetry of performance in the Landmark task. This implies that performance of a cognitive function can, at least to some extent, be predicted by anatomical markers of the functional network. Consequently, researching hemispheric lateralization and its origins is of great importance for our better understanding and prediction of behaviour.

**Face Processing**

Face processing is a function that has reportedly been disrupted by lateralized brain damage. Prosopagnosia is a dysfunction in face recognition that can manifest itself in various forms and can both be acquired and congenital (Kennerknecht et al., 2006).
De Renzi, Perani, Carlesimo, Silveri and Fazio (1994) examined prosopagnosic patients with lesions confined to the right occipito-temporal lobe and hypometabolism of the right hemisphere exclusively, as confirmed by positron emission tomography (PET). Moreover, they reviewed literature describing 31 cases of prosopagnosia associated with right hemispheric damage. However, prosopagnosia did not manifest in the majority of individuals with occipito-temporal damage. De Renzi et al. (1994) concluded that individuals differ in the degree of RH specialization in face processing, with only a minority unable to compensate by means of the healthy left hemisphere. Nevertheless, we can state that face recognition typically seems to depend mostly on, and seems to be most specialized in the right hemisphere. Kennerknecht et al. (2006) concluded that lesions leading to acquired prosopagnosia can be either bilateral or unilateral, but when unilateral, they are almost always located in the right hemisphere. Apperceptive prosopagnosia is the most severe form of prosopagnosia in which individuals fail to recognize any face or facial characteristics with visual processes intact. Lesions responsible for this form are located mainly in right occipital temporal areas. Individuals with associative prosopagnosia fail to recognize familiar faces, or are unable to integrate processed facial characteristics with semantic information about the person associated with the face. Right anterior temporal lesions are most commonly responsible for this deficit (Gianotti, & Marra, 2011).

There are various tasks that specifically require face processing and are used to examine this function in normal subjects. In accordance with findings from prosopagnosic patients, healthy subjects have a left visual field, and therefore right hemispheric, advantage in reaction times for deciding whether or not laterally presented stimuli constitute faces (Hay, 1981). Young (1983, 2012) reviewed evidence concerning functions of the right cerebral hemisphere and linked more efficient processing of physical and emotional facial information to the right hemisphere. Rhodes (1993) stated that expertise in recognizing faces is associated with configural coding, and configural coding is associated with a right hemisphere advantage. Therefore, face recognition is lateralized to the right hemisphere. This rationale was supported by research of Rossion et al. (2000) several years later. They found that the right middle fusiform gyrus was more activated during a whole, or configurally coded, face matching task. When participants were required to match parts of faces, on the other hand, the left middle
fusiform gyrus was more activated. Sergent, Ohta, & Macdonald (1992) dissociated processing faces from objects by showing that face recognition tasks mainly activated right ventro-medial and right occipito-temporal regions, whereas object recognition tasks mainly activated left occipito-temporal regions. Kanwisher, McDermott, and Chun (1997) confirmed these findings and named the occipito-temporal region in the right fusiform gyrus selectively activated by faces the right Fusiform Face Area (FFA). Pitcher, Walsh, Yovel, and Duchaine (2007) provided transcranial magnetic stimulation (TMS) evidence for the fact that right inferior occipital gyrus, or the right occipital face area (OFA), is involved in early stage face processing as well. Fox, Iara and Barton (2009) examined functional localization of the face processing network and found that dynamic facial stimuli were optimal to engage core face processing regions. These regions were the FFA, the OFA, and the posterior superior temporal sulcus, all of which were predominantly activated in the right hemisphere. Whether areas such as the FFA are specific to faces or rather specific to highly trained visual stimuli in general is still a question of debate. However, we can conclude that face processing provides us with robust evidence of a laterized cognitive function. Therefore, it is pragmatically interesting to employ face processing in order to study hemispheric specialization.

**Origins of Hemispheric Specialization**

There is a specific pattern of lateralization of cognitive functions in the majority of the population. Spatial attention and face processing typically predominantly rely on the right hemisphere. The possibility of spatial attention and face processing predominantly involving the left hemisphere in a fraction of the population should not be excluded either. However, it is unclear what processes underlie the direction of functional lateralization, and functional lateralization in general. Pinel and Dehaene (2010) attribute the development of functional asymmetries to phylogenesis and ontogenesis. Phylogenesis is the evolutionary development and diversification of a species or group of organisms, or a particular feature of an organism. Ontogenesis, on the other hand, is the development of an individual organism or feature from the earliest stage to maturity. Furthermore, there are multiple possibilities within phylogenetic and ontogenetic mechanisms as to what might influence the development of functional lateralization.
Cai, Van der Haegen and Brysbaert (2013) illustrated an evolutionary origin of hemispheric functional lateralization, with an emphasis on its benefits. When looking into the mechanisms underlying hemispheric specialization, we can wonder what the evolutionary advantages are. Cai et al. (2013) stated that the distribution of functions to different hemisphere avoids ‘crowding’, a term used in the crowding hypothesis putting forward the notion that one cognitive function can be overshadowed by another one if they are mostly dependent upon the same hemisphere (Kosslyn, 1987). Rogers, Zucca and Vallortigara (2004) argued that “cerebral lateralization enhances brain efficiency in cognitive tasks that demand the simultaneous but different use of both hemispheres”. This way, disparate functions can operate in parallel, and therefore take less time to complete. Alternatively, some functions might share the same origin and benefit from similar lateralization in order to share the same lateralized resources. As Pinel and Dehaene (2010) stated, co-lateralization might constitute evolutionary traces on how these mental abilities evolved. Another possible advantage is the avoidance of useless duplications. More specifically, if both hemispheres would perform the same cognitive process and subsequently communicate, a lot of processes might needlessly be performed in duplicate prior to communication between the hemispheres. Moreover, simultaneous activation of incompatible responses in duplicated functional regions can result in a conflict that can easily be resolved by means of one specialized or dominant hemisphere. The specific pattern, or direction, of functional lateralization might be due to a dominant genotype. Typical cognitive asymmetries can be favoured by this dominant genotype, allowing for less expression of an alternative genotype coding for atypical cognitive asymmetries.

If assuring that two cognitive functions do not demand simultaneous but different use of both hemispheres, avoiding useless duplications, and avoiding ‘crowding’ are reasons for the pattern of functional asymmetries in the brain, it may be useful to take into account the type of functions that are involved. Some cognitive functions will inherently coincide in the timing and extent of their demands much more often than others. And some cognitive functions might benefit from activating different hemispheres, whereas others might benefit from activating the same hemisphere without needlessly activating the other as well. Cai, Van der Haegen and Brysbaert (2013) reasoned that the lateralization of language and spatial attention are dependent because
both functions perform better with a single unilateral control, which avoids crowding. Accordingly, the epicentre of spatial attention is located in the left hemisphere in individuals where the epicentre of language is located in the right hemisphere, and vice versa. Vingerhoets et al. (2013) found that atypical language dominance can significantly predict the occurrence and degree of atypical dominance for praxis, i.e. right hemispherical as well, and vice versa. Vingerhoets et al. (2013) concluded that hemispheric specialization might be grounded in an evolutionary remnant of complex learned movement, a neural system out of which tool use, sign language and speech evolved. This way, the lateralization of both praxis and language processing to the same, typically left, hemisphere, can be explained, as they both stem from complex learned movement and useless duplications are avoided. The findings of both Cai et al. (2013) and Vingerhoets et al. (2013) support the causal hypothesis of lateralization, stating that functions lateralize accordingly. More specifically, the causal hypothesis states that asymmetry of cognitive functions are dependent upon each other. The direction and degree of lateralization of one function can therefore predict the direction and degree of lateralization of another function.

However, there is also deflecting evidence for the causal hypothesis and in favour of the statistical hypothesis, according to which functions lateralize independently. More specifically, the statistical hypothesis argues that the hemispheric asymmetry of one cognitive function is independent of, and therefore unpredictable by, the asymmetry of another function. This implies that when a cognitive function lateralizes atypically, this is no reason for another function to lateralize atypically as well. This is exactly what Flöel et al. (2001) found in their study concerning language processing and spatial attention. They stated that language and spatial attention can lateralize to the same hemisphere in healthy humans. In a later study, Flöel et al. (2005) concluded “The cerebral cortex seems to possess the capacity to organize cognitive functions in a pattern different than the ‘standard’ pattern, in the absence of brain damage and without apparent behavioural costs”. The statistical hypothesis is in accordance with some potential advantages of and reasons for functional lateralization. If cognitive functions lateralize independently, useless duplications and simultaneous activation of incompatible responses are avoided. Parallel processing is enabled to some extent according to the statistical hypothesis as well, albeit without taking into account
which cognitive functions might require the most parallel processing. Moreover, ‘crowding’ would be avoided in a general manner, since distribution of any functions to different hemispheres can shun one function overshadowing another. However, ‘crowding’ is not avoided in a way that takes into account the specific nature of the involved cognitive functions or how they would or would not demand simultaneous and similar cognitive mechanisms.

Pathology and environmental mechanisms can influence functional asymmetry as well. Provins (1997) pointed out that functional dominance to one cerebral hemisphere should not be assumed to be due to predetermined and inborn causes only. For instance, epileptic disorders can influence lateralization of cognitive functions such as memory (Detre et al., 1998; Janszky et al., 2004). Likewise, Cowell, Waters, and Denenberg (1997) demonstrated that the presence or absence of handles in early environment has an effect on the development of functional laterality of spatial cognition in rodents, as measured by performance in a Morris maze. Another well-known phenomenon of the influence of environment on the direction of lateralized functionality is left handedness. Since left handedness was often discouraged in early childhood education until recently, many individuals who were initially left handed, are now right handed, with its possible implications on the extent and direction of functional lateralization of praxis in the brain.

Considering all potential causes for the development of functional asymmetries, an important option to further explore is anatomy. An accessible inference might be that functional asymmetry stems from anatomical asymmetry in the brain. As previously mentioned, the brain is asymmetrical in its anatomy. Brain anatomy concerns the amount of grey matter, white matter, and connectivity. These factors undoubtedly influence brain function. Andreasen et al. (1993) and Colom et al. (2009) illustrated this by showing that the amount of grey matter in certain cortical areas, such as the dorsolateral prefrontal cortex, accounts for variance in human intelligence and spatial cognition. Blakemore (2008) stated that structural development - such as synaptic reorganization of social brain regions including medial prefrontal cortex and superior temporal sulcus - during adolescence coincides with changes in brain function and behaviour - such as face recognition. Furthermore, Blakemore (2008) considers a useful approach for future research to be looking into correlations between structural and
functional individual differences, since as yet, no such research is available concerning social brain functions. Studying a possible structural influence on the lateralization of a cognitive function such as face recognition within individuals may therefore prove to be very interesting. Paus et al. (2001) came to a similar conclusion concerning the need to study structure-function relationships. They found that white matter increases in volume with age, and becomes more myelinated in a region-specific fashion. A suggestion for future directions of research was made, with an emphasis on the concurrent use of structural imaging, behavioural testing and functional imaging.

Another plausible account for the development of functional asymmetries in the brain is that both brain anatomy and functionality are caused by the same the same phylogenetic and ontogenetic mechanisms. Most probably there is an evolutionary benefit to both anatomical and functional asymmetry, resulting in lateralization over generations. Perhaps anatomical and functional lateralization are coded by certain shared genes. Glahn, Thompson, and Blangero (2007) studied neuroimaging endophenotypes - phenotypes with a clear and established genetic connection, which are used to link symptoms and genes - and found that they are quantitative indicators of both brain structure and function. Factors such as sex and age can also be a shared direct influence on brain anatomy and function. Raz (2000) integrated structural and functional findings and concluded that the aging of the brain affects both its anatomy and function.

In conclusion, concerning the role of anatomy in the lateralization of cognitive functions, there are two important potential accounts. Firstly, functional asymmetries may be caused by anatomical asymmetries, which in turn may be the result of numerous underlying mechanisms. Secondly, functional and anatomical asymmetries may share the same basis, both being caused by the same mechanisms. Whereas the first possibility only links the fundamental mechanisms underlying anatomy indirectly to functional asymmetry, the latter possibility directly links the two in the causal chain. Most probably both possibilities partially account for the development of functional asymmetry. Regardless of which account represents reality, it is important to consider which mechanisms potentially underlie brain anatomy and therefore its extent and direction of asymmetry.
Structural asymmetry may be influenced by multiple factors. The right anterior petalia and left posterior petalia in the majority of the population might originate from an evolutionary benefit. Perhaps they are the result of a dominant genotype, allowing for less expression of recessive genes coding for another shape of petalia. Peper et al. (2007) studied the genetic influences on human brain structure by means of reviewing brain imaging research in twins. They found that variation in brain volume is genetically influenced, with high heritability estimates for grey matter density in medial frontal cortex (±90%) and moderate heritability estimates in hippocampal areas (±60%). More specifically, they reported these heritability rates for grey matter of frontal cortex, postcentral gyrus in the parietal cortex, parahippocampal gyrus in the inferior temporo-occipital cortex and Broca’s area, and white matter of the occipitofrontal fasciculus. Since spatial cognition predominantly involves a frontoparietal network (Çiçek, Deouell, & Knight, 2009), face processing predominantly involves occipito-temporal regions (Fox, Iaria, & Barton, 2009), and Broca’s region is highly involved in language processing, these findings might relate to functional asymmetries as well. Other factors that can potentially underlie differences in brain anatomy are sex and lateralization in functionality or behaviour, such as handedness. Good et al. (2001) researched cerebral asymmetry and the effects of sex and handedness on brain structure by means of voxel-based morphometry in 465 normal adults. They found that there was a significant effect of sex on brain morphology and structural laterality. However, there was no main effect of handedness, nor any interaction between asymmetry and handedness. This suggests that lateralized behaviour or functionality is unlikely to influence brain structure. Sex, however, seems to have an influence on brain structure. Peper et al. (2007) pointed out another important factor in the development of hemispheric lateralization of anatomy, being environmental influences. In their review of twin studies they stated that environmental factors impact several medial brain areas. Importantly, the possibility that functionality alters anatomy should not be excluded either. The study of Good et al. (2001) showed that lateralized behaviour or functionality such as handedness does not seem to influence brain structure. However, an illustration of the effect of brain function on brain structure was provided by McEwen (2005) and Drevets, Price, and Furey (2008). The study of McEwen (2005) showed that mood disorders influence brain structure, whereas the latter study states that mood disorders influence brain function.
Brain function is often disrupted by mood disorders without any detectable effect on brain anatomy. The reversed pattern, with brain anatomy being affected by mood disorders before brain function, is not observed. Therefore, mood disorders may have an indirect effect on brain structure by means of a direct effect of brain function. Epilepsy is another example of a functional deficit which may affect brain structure, for instance by causing increase in frontal grey matter in subjects with juvenile myoclonic epilepsy (Woermann, Free, Koepp, Ashburner, & Duncan, 1999).

The anatomy of the brain can also directly be influenced during embryogenesis because of pathology or an atypical genotype, impacting lateralization of brain structures. Situs Inversus (SI) is a congenital condition in which visceral organs are mirrored compared to their normal positions, which is Situs Solitus (SS). SI is generally an autosomal recessive genetic condition (Gedda et al., 1984). About one fourth of individuals with SI have an underlying genetic disorder known as primary ciliary dyskinesia (PCD). PCD is a dysfunction of the cilia, manifesting early in development. Cilia are small hair-like organelles in eukaryotic cells that protrude the cell body. It has been shown that proper cilial function is responsible for the typical left-right anatomical asymmetry in mammals (McGrath, & Brueckner, 2003). Because of PCD, the cilia are not able to function properly and will therefore not determine or differentially determine the position of internal organs. This causes half of the individuals with PCD to develop SI. The phenomenon of individuals with PCD developing SI is called Kartagener syndrome. SI is found in approximately 0.01% of the population and most individuals with SI have no serious medical complications resulting from the condition. Moreover, SI was usually undiagnosed before modern medicine and still remains undiagnosed occasionally nowadays. Nevertheless, cardiac problems occur more often in SI than in the normal population and individuals with Kartagener syndrome may have additional problems. Since cilia are also responsible for multiple other functions, individuals with PCD often have chronic sinusitis and bronchiectasis. Additionally, there is increased susceptibility to lung infections and male infertility, as the flagellum of human sperm is a modified cilium.
Structure-function relationships in hemispheric specialization: Situs Inversus

The question remains what most determines the extent and direction of cognitive asymmetries in the majority of the population. It would be interesting to research whether a change in the lateralization of brain structure alters the lateralization of cognitive functions. Unfortunately, an experimental manipulation of the lateralization of brain structure is infeasible. Situs inversus (SI) is a condition that most closely approaches an exclusive manipulation of the lateralization of anatomy. Neuropsychology, the area of research comparing individuals with a brain injury or atypical brain to normal controls, can expose potential critical factors in certain brain functions. Looking into individuals with SI would be most interesting since this allows us to explore the link between an inverse position of visceral organs, a possibly inverted position of the brain and possible differences in functional hemispheric lateralization. Moreover, aside from providing new insights into the origins of hemispheric specialization, research on SI might be able to provide new insights into structure-function relationships in general.

It is important to note that the phenotype - an observable characteristic resulting from the combination of expression of genes and environmental influences - of SI may be the result of many different factors. In the interest of approximating a manipulation of only the lateralization of anatomy, it is necessary to clarify when this would be obtained. The literature concerning the typical direction of anatomical lateralization concerns an average and the majority of the population (Kennedy et al., 1999; Ihara et al., 2010; Good et al., 2001). Needless to say, there are individuals who naturally deviate from this normality. When an individual has the phenotype of SI because of natural genetic disposition, it is quite probable that the underlying mechanisms resulting in this atypical anatomical lateralization also affect functional lateralization. Accordingly, an atypical lateralization of cognitive functions may very well be the result of underlying mechanisms shared between anatomy and brain function, instead of being the result of atypical structural asymmetries. Therefore, conclusions concerning the causal link between structural asymmetries and functional asymmetries in these individuals are rather unadvisable, since there is a substantial increase in the amount of confounding variables. These individuals would, however, remain interesting to study, since a correlational result can still provide pragmatic information even though there is
no direct causal link. Anyhow, individuals with diagnosed SI are often only diagnosed because of the mentioning of secondary complaints associated to primary ciliary dyskinesia (PCD). Therefore, any research on individuals with SI would have a high prevalence of Kartagener syndrome, or unnaturally occurring SI due to pathology in genotype. When an individual has Kartagener syndrome, or the co-occurrence of PCD and SI, more reliable conclusions can be made. Since PCD is a deficit affecting the cilia, the probability of the underlying mechanisms resulting in the atypical anatomical asymmetries affecting functional asymmetries as well is quite low. Thus far, there is no research implicating cilia in the development of functional lateralization. Therefore, the phenotype of SI will most probably be the manifestation of atypical structural asymmetry exclusively, where functional asymmetry would have developed in a typical fashion if it were not influenced by anatomy.

We can expect that, if an individual has Kartagener syndrome and mirrored brain anatomy, and if functional asymmetry is 100% dependent upon structural asymmetry, hemispheric specialization of cognitive functions will be inversed compared to the typical pattern. And when an individual has Kartagener syndrome and mirrored brain anatomy, and if functional asymmetry is 100% independent from structural asymmetry, hemispheric specialization of cognitive functions will not be inversed compared to the typical pattern. However, firstly, when researching individuals with mirrored visceral organs, information about the anatomic lateralization of the brain is not always provided. Secondly, it is not always possible to know with 100% accuracy whether PCD is involved. And since the phenotype of SI, as well as hemispheric specialization, may have multiple causes, a mixed outcome is more probable. Even when targeting individuals with Kartagener syndrome exclusively, a mixed outcome is most realistic. Considering all the previously mentioned potential causes of functional asymmetry, it is most probable that functional lateralization is only partially dependent upon anatomical lateralization. Moreover, there is a natural variation of the direction of hemispheric specialization of cognitive functions in the population, even without focusing on individuals with SI. Therefore, the outcome might not be as expected when considering only typical functional asymmetry.

Nevertheless, if functional asymmetry in the brain is partially dependent upon structural asymmetry, the lateralization of cognitive functions in individuals with SI
should be atypical or inversed more often than in normal SS controls. Therefore, researching hemispherical lateralization of asymmetrical cognitive functions, such as spatial cognition and face processing, in individuals with SI, would be very interesting. It may provide us with crucial information about the development of functional asymmetries and the anatomical foundations of cognitive functions. Notwithstanding, only a poor amount of research concerning this topic has been reported in the literature as yet.

Matsumoto et al. (1997) excluded a significant relationship between handedness and visceral position by stating that incidence of right handedness and right footedness in individuals with SI was consistent with the incidence in the normal population. They concluded that “the development of the brain appears to be independent of that of the viscera, in organogenesis, during the course of human embryonic development”. The main problem with this study is the underspecification of which aspects of the development of the brain they intent to discuss. Findings related to a lateralized behaviour such as handedness should not qualify to infer conclusions about development of brain anatomy, for instance. Kennedy et al. (1999) found that the petalia in individuals with SI were reversed in their anatomical position compared to individuals with situs solitus (SS). However, the laterality of largest planum temporale (PT) volume in subjects with SI was found to be the same as in SS. They also inquired into the direction of the interhemispheric fissure between the occipital lobes and results indicated no dominant direction in individuals with SI, while the dominant direction in normal subjects was rightward. Concerning functionality, the results of the study of Kennedy et al. (1999) yielded a left hemispheric dominance for language in SI as well as in SS. Their results indicated that, while there are some anatomical differences in brain asymmetry in individuals with mirrored visceral organs compared to controls, these do not coincide with functional dominance differences in the domain of language. Tanaka, Kanzaki, Yoshibayashi, Kamiya and Sugishita (1999) examined the Standard Dichotic Listening Test in subjects with SI and matched controls who were all strongly right handed. Their results indicated that 8 out of 9 participants with SI reproduced sounds from their right ear more often than sounds from their left ear, also known as a right ear advantage. Similarly, 19 out of 24 subjects in the control group showed right ear advantage. Tanaka et al. (1999) concluded that “results of the present study suggest
that the left-right reversal in SI does not involve functional asymmetry of the brain. As such, the system that produces functional asymmetry in the human brain must independently recognize laterality from situs asymmetry”. Lastly, in a more recent study, Ihara et al. (2010) found that the laterality of largest petalia in individuals with SI was reversed compared to controls. The asymmetry of largest planum temporale (PT) volume in subjects with SI was found to be the same as in individuals with SS. The latter two findings are in accordance with the study of Kennedy et al. (1999). However, in contrast to the report of Kennedy et al. (1999), Ihara et al. (2010) found right hemispheric dominance for language in 2 out of 3 individuals with SI. The remaining subject with SI displayed, like all controls, left hemispheric dominance for language. Additionally, they inquired into the amount of grey matter in the inferior frontal gyrus (IFG), which was found to be inconsistent in laterality for both groups. However, both SI subjects who had right hemispheric language dominance had a rightward IFG as well. Ihara et al. (2010) concluded “These results suggest that the developmental mechanisms underlying visceral organ asymmetries are related to those underlying petalia asymmetry, but are unrelated to those underlying PT and IFG asymmetries”.

Out of the existing literature we can conclude that further research is necessary. The sample size in most previous studies was very limited and adequate control subjects were not present in every study. The scope of functional asymmetry in all studies was narrow as well. More specifically, only the dominantly left lateralized network of language was considered, while there are various other networks of brain functions that are represented asymmetrically in the normal brain. It may be interesting to look at dominantly right hemispheric functions, such as face processing and spatial attention, as well. In the current study, we wish to research hemispheric specialization in individuals with SI to a greater extent. An increased sample size, adequate control participants, and a broader scope of cognitive functions will be applied. Thus, we hope to uncover more about the mechanisms that may be involved in the development of cognitive asymmetries. It is presumable that the results of the current study will provide evidence for mechanisms involved in this development depending on the brain region and functional network involved, rather than a universally applicable explanation for the development of whole-brain functional asymmetries. Nevertheless, it may result in crucial information about structure-function relationships. We expect to find that there
is a higher prevalence of atypical hemispheric specialization of face processing and spatial cognition in individuals with SI due to the fact that anatomy is one of the factors that lie at the basis of cognitive functions.

**METHOD**

**Participants**

Voluntary subjects with SI and matched controls for these subjects (SS) participated in the study. Control participants were selected based on sex, age, handedness, and education. In the analysis for this thesis, 12 subjects with SI (19-50 years old, 7 male – 5 female, 4 left handed – 8 right handed), and 12 matched controls (18-50 years old, 7 male – 5 female, 4 left handed – 8 right handed) were included. Subjects were assigned a number to identify them without exposing their personal information. SI participants were indentified based on granted limited access to medical files of the university hospital of Ghent and Antwerp, stating they had inversed organization of visceral organs. 4 of the 12 participants (SI6, SI8, SI11, and SI15) have diagnosed Kartagener syndrome, which is the co-occurrence of SI and PCD. 4 other participants have medical complaints associated to Kartagener syndrome, but are undiagnosed (SI3, SI5, SI13, and SI14). All participants were provided an informed consent and granted an endowment for participation in this study. SI subjects were granted €200 and control subjects were granted €100 for participation.

**Design**

The main independent between-subjects variable examined in this study is the situs of the participant, being situs inversus (SI) or situs solitus (SS). Evidently, experimental manipulation of this nominal independent variable is impossible, since it is found naturally in the population. Other independent within-subjects variables, which are susceptible to experimental manipulation, are the different conditions in the tasks representing the lateralized functional networks of spatial cognition and face processing, the landmark task and the face recognition task. Both tasks have their own embedded design. The independent within-subjects variables in the landmark task are the line position, and the control vs. active condition. The independent within-subjects variables in the face recognition task are the change vs. repetition of the stimulus, and the face vs.
object condition. The dependent variable in both tasks is the extent of lateralized activation of functional regions of interest during task performance in different conditions.

**Other aspects of this study**

Aside from the tasks employed to research the lateralized functional networks that are the main focus of this thesis, a word generation task and a pantomime task were employed in this study as well. These tasks inquire into the functional network of language and praxis, and their design will also be discussed shortly. Moreover, functional imaging was merely one aspect of this study in its whole. To broadly examine brain function in individuals with SI compared to individuals with SS, anatomical imaging, behavioural testing and genetic sampling were employed as well. Aside from the main anatomical imaging, none of these other methods of research were employed to examine the main research question of this thesis. For a complete overview, these other aspects of the study are shortly mentioned, but will be of no further interest in this thesis.

**Procedure and Materials**

*Genetic Sample.* Firstly, a genetic sample of participants with SI was taken by means of saliva. Subjects were also asked to deliver a genetic sample of both or one of their parents. Thereby, potential genetic factors contributing to the lateralization of functional networks can be assessed.

*Behavioural Data.* Subsequently, participants submitted neuropsychological tests and questionnaires. For an estimation of the intelligence quotient (IQ), the Nederlandse Leestest voor Volwassenen (NLV, Schmand, Lindeboom, & van Harskamp, 1992) was assessed. The NLV relies on the aloud pronunciation of irregularly pronounced words. This provides an estimation of the premorbid IQ, since the test is insensitive to cerebral damage. In the current study, however, we used the NLV mainly because it allows for an accurate estimation of IQ within a short time span. If the participant did not speak Dutch and was therefore unable to perform the NLV, the Raven’s Progressive Matrices (RPM, John Raven) were employed. The RPM allows for a culture-free estimation of IQ. Subsequently, by means of the Lateralisatie Voorkeur
Protocol (LVP, Vingerhoets), the dominant laterality of hand use, foot use, ear use, and eye use was assessed. Moreover, participants were questioned about possible external compulsion to use their non-dominant hand and about possible familial sinistrality, or left handedness. Thirdly, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, Randolph, Tierney, Mohr, & Chase, 1998) was assessed. The RBANS consists of 10 subtests which give scores for five domains, more specifically, immediate memory, visuospatial/constructional, language, attention and delayed memory.

Anatomical Neuroimaging and Resting State. All imaging was conducted in a 3 Tesla Siemens Trio Tim MRI scanner. Detailed anatomical scans, resting state functional imaging scans and diffusion tensor imaging scans were carried out. All scans were conducted by means of magnetic resonance imaging (MRI). The functioning of a MRI scanner depends on three main components, a magnet, gradient coil magnets and a radio frequency coil. The magnet creates a magnetic field and requires extensive cooling by means of liquid helium. The gradient coil magnets create different and varying magnetic fields and the radio frequency coil transmits and detects radiofrequency waves. Atoms with an uneven number of protons act as dipoles, or small magnets, and will automatically align in a strong static magnetic field, as supplied by the magnet. Hydrogen (H\textsubscript{2}O) has an uneven number of protons and is highly present in the human body. Due to the spinning protons, hydrogen will align with the main magnetic field supplied by the magnet. The protons now have an alignment and spin that is related to the strength of the magnetic field. The radio frequency coil will put in a radio frequency that matches the speed at which the protons spin, called the Larmor frequency. Consequently, the protons absorb this energy and get deflected 90° out of alignment with the magnetic field, by which they enter a high energy state. However, the protons prefer a low energy state and will get back in alignment with the main magnetic field, returning radio frequency energy. The time to get back in alignment is referred to as the T\textsubscript{1} time or spin-lattice relaxation time. Since some protons spin faster or slower than others, they will start dephasing after the 90° pulse, whereby the signal loses its coherence. The time it takes to dephase is called the T\textsubscript{2} time or the spin-spin relaxation time. The T\textsubscript{1} time and the T\textsubscript{2} time depend on the tissue involved. Various pulse sequences can be employed to enter radio frequency by means of the gradient coil.
magnets and adjust the magnetic fields, and therefore Larmor frequency. This way, location specific activations can be measured and structural images can be obtained. The time between two consecutive radio frequency pulses is the repetition time (TR). Subjects completed a MRI-safety questionnaire before participation.

**Functional Neuroimaging.** In order to localize lateralized networks for certain functional tasks, functional magnetic resonance imaging (fMRI) was implemented. fMRI relies on the mechanisms of MRI but uses another measurement that is related to the T2 time, the T2* time. A 180° refocusing pulse minimizes the T2 time or 'going out of alignment' effect. T2* time is the component that does not refocus, little microscopic distortions of the magnetic field that remain. T2* time also depends on the tissue that is involved. Blood carries hemoglobin (Hb), an iron-containing oxygen-transport protein in red blood cells. Iron can distort the magnetic field and has slightly different magnetic properties depending on whether it is bound to oxygen (OxyHb) or not (DeoxyHb). If blood contains more OxyHb, the dephasing and T2* time will be slower, whereas if blood contains more DeoxyHb, the dephasing and T2* time will be faster. Different brain states are associated with regional changes in the brain’s oxygen utilization. Since neurons depend on neurovascular coupling to supply oxygen in the brain for their activity, we can infer activity of the brain from the Blood-Oxygenation Level-Dependent (BOLD) signal. The BOLD signal relies on the ratio between OxyHb and DeoxyHb, more specifically: the higher the OxyHb level, the stronger the signal. The BOLD signal is assumed to follow the Hemodynamic Response Function (HRF), which follows the adjustments in blood flow to deliver nutrients to stressed tissues and causes the temporal resolution of fMRI to be limited as it is rather slow. The TR in this study was 2500ms, which suffices to capture a slow response to stimuli with a presentation time of up to 2000ms, but is not too long in order to avoid an insufficient temporal resolution. The spatial resolution of fMRI is determined by the size of the individual measured spatial elements which are used further on for statistical testing, voxels. The voxel size in the current study is 3mm x 3mm x 3mm.

To inquire into the laterality of the functional network of language, fMRI was assessed during the Word-Generation task (Cai, Van der Haegen, & Brysbaert, 2013). Participants were asked to silently produce as many words as possible, starting with a specific displayed letter. In the control condition, participants had to silently repeat the
nonword “baba”. The laterality of the functional network of praxis was assessed by means of fMRI during the Pantomime task of Vingerhoets et al. (2012). During this task, subjects were asked to pantomime unimanual and bimanual tool using actions with either hand or both hands. As a control for transitive pantomime movements in general, they were asked to perform unimanual and bimanual actions unrelated to tool-use with either or both hands on eggs.

For the assessment of the laterality of the functional network of face processing, the Face Selective Dynamic Localizer task (Fox, Iaria, & Barton, 2009) was implemented during fMRI. Participants performed a ‘one-back’ task during which they were instructed to press a button if a short video clip was identical to the previous one. During this so-called ‘dynamic localizer’, video clips of non-living objects and faces were presented in separate blocks. Video clips of faces displayed dynamic changes in facial expression, each starting from a neutral expression and ending in a basic emotional facial expression. An example of a block of facial expressions is presented in Figure 1. As a control condition, video clips of objects displayed dynamic changes in the object that were comparable to facial expressions concerning the absence of large translations in positions, for example: a fountain spraying, a globe spinning, and fireworks exploding. Thus, confounding basic visual factors, affecting the difference between dynamic faces and objects in a manner other than by their conceptual nature, were avoided. The task began and ended with a fixation block, in which a cross was displayed in the centre of the screen. Additionally, image blocks were altered with fixation blocks. There were eight counterbalanced blocks of each stimulus category, object and face. Each image block consisted of 5 novel and 1 repeated video-clip, each presented for 2000ms. The dynamic localizer took 396 seconds in total.
The Landmark task of Çiçek, Deouell, and Knight (2009) was implemented to examine the laterality of the functional network of spatial cognition. Stimuli consisted of prebisected lines and subjects were instructed to indicate whether or not the lines were correctly bisected by pushing a button. In 40% of the trials, bisection marks were placed at the true midline. In the remaining 60% of the trials, bisection lines deviated to the right or left of the midline by 2.5%, 5% or 7.5% of the line’s length. The percentage of correct responses represented performance scores. In the control condition, stimuli consisted of lines with an adjacent (40% of the trials) or separate (60% of the trials) mark and participants were required to indicate whether the mark touched the line or not. Figure 2 displays the stimuli of the Landmark task.

**Figure 1.** Example of a Facial Expressions Block in the Face Selective Dynamic Localizer task (Fox, Iaria, & Barton, 2009).

**Figure 2.** Stimuli of the Landmark task in the Active and Control condition (Çiçek et al., 2009)
**fMRI Data Analysis**

All fMRI data preprocessing and analysis was performed in BrainVoyager QX 2.4. Raw fMRI data should not directly be statistically analyzed because of the influence of artefact and noise-related signal components. More specifically, it is essential to exclude the possibility that signal changes due to factors that are unrelated to the experimental conditions of interest are misinterpreted as being signal changes of interest. Therefore, fMRI data is preprocessed. A first step in fMRI data preprocessing is slice scan time correction. The whole brain is not scanned at once as a functional 3D volume, but rather by means of several successively scanned 2D slices. Unfortunately, these individual slices are usually not scanned simultaneously and therefore differ in timing. Usually, one measure of all slices is recorded within on repetition time (TR). The TR employed in the current study is 2500ms. Hence, the slice that was recorded first can differ up to 2500ms in timing compared to the last recorded slice. Even though the temporal resolution of fMRI is inherently low due to the slow HRF, it is important to be as precise as possible in timing when researching event-related signals. In order to avoid these suboptimal conditions, we can shift the recorded data of the individual slices to the same timing of when the reference slice was recorded. This data-shifting approach allows for event-related responses in certain brain regions of interest to be analyzed correctly with respect to certain task conditions and their respective timing. In order to shift the data of a slice, a measured data-point, to the reference point, resampling of the data is required. Values of data at non-measured time points can be interpolated from data at measured time points. Cubic spline interpolation was applied, which uses more than the data of the two nearest measured time points, allowing for accurate resampling.

A following step in preprocessing fMRI data is motion correction. Motion correction allows for correction of small head movements (up to about 5mm) by means of aligning functional volumes to one reference volume. Since the brain can be considered as a rigid body, its displacement can be corrected by means of 6 parameters, more specifically translation and rotation in the 3-dimensional space. However, head motion can distort the specific induced magnetic field and should therefore be avoided. Motion correction evaluates the goodness-of-fit of difference in intensity values of
corresponding positions compared to the reference volume and tries to find a minimum of difference in a nonlinear least-squares approach using trilinear spatial interpolation. The final motion parameters in comparison to the reference volume are applied to the functional volume and a new volume is created by means of sinc spatial interpolation. A following critical step in preprocessing fMRI data is temporal high-pass filtering, or the removal of linear and nonlinear trends. Due to noise, fMRI data often show low-frequency drifts that can have a substantial effect on statistical data analysis. A temporal high-pass filter that is applied to each voxel’s time course preserves the high frequencies in the signal and removes the low frequencies. Thus, stimulus-related activity is preserved while signal drifts are removed. High-pass filtering in Brain Voyager was performed by means of a GLM approach with Fourier basis set and 2 cycles.

In order to be able to compare between subjects, the brain data needs to be transformed into a common, normalized space. In the current study, we will use Talairach space, a 3-dimensional coordinate system of the human brain based on the location of the anterior commissure (AC) and posterior commissure (PC). The AC-PC line is placed horizontal and the plane formed by this line on the midsagittal plane is required to be vertical. The AC is considered the origin of the Talairach space. The x-axis is directed left-right, the y-axis is directed anterior-posterior, and the z-axis is directed ventral-dorsal. The left, right, anterior, posterior, inferior, and superior cortical outlines of the brain are identified as well. Firstly, the preprocessed functional data set was coregistrated with the anatomical dataset to make sure different placement or small head movements do not cause a difference between the anatomical and functional data. This was accomplished by means of automatic initial alignment and full alignment. The functional data set is rotated and translated to closely approximate the global orientation of the anatomical dataset in the initial alignment. During full alignment this coregistration is fine-tuned. Subsequently, the anatomical brain data was normalized and manually transformed into Talairach space by means of sinc interpolation. Finally, the functional data was linked to the normalized anatomical space in order to create volume time course (VTC) data files. Converting the functional data to VTC data is accomplished by means of using the normalized anatomical data and functional-anatomical coregistration data.
After creation, the VTC data files were preprocessed. More specifically, a Gaussian function with a Full Width at Half Maximum (FWHM) of 8mm was convolved with the fMRI signal for spatial smoothing. This way, high frequencies are removed from the data and low frequencies are enhanced, enabling higher spatial correlation. Spatial smoothing is applied to functional fMRI data before statistical analysis to increase sensitivity and improve the signal to noise ratio (SNR), to increase the overlap between anatomical and functional variations between subjects, and to improve the validity of statistical tests by means of assuring the assumption of a normal error distribution. Since we will be researching spatial characteristics of certain lateralized brain functions, a strongly reduced spatial resolution might not seem like an advisable option. However, if the FWHM is set too small, there is no substantial effect on the SNR while spatial resolution is still reduced. Another drawback of spatial smoothing is potentially losing information about small meaningful activations in the brain, but is is nevertheless a necessity.

Hypothesis-driven statistical analysis of the fMRI data was enabled by means of the General Linear Model (GLM). The GLM is suitable to analyze fMRI data because it is a form of multiple regression analysis that allows incorporating multiple categorical, or qualitative, and continuous, or quantitative, independent variables. We want to localize the dominant hemisphere involved in lateralized brain functions and are therefore interested in the difference in a lateralized activity pattern during different conditions in individuals with SI compared to individuals with SS. Differences in the activity pattern can, however, also be random and due to physical and physiological noise. By means of the GLM it is possible to incorporate information about any variable that can have an effect on the dependent measure of interest. Thereby, true differences in the signal due to the experimental conditions of interest can be assessed if they are unlikely solely due to the modelled noise variables.
Figure 3. GLM system of equations.

Statistical analysis was performed for each voxel independently, i.e. the GLM was applied in its univariate version for each voxel with the voxel time series as the dependent variable. The objective of the GLM is to account for the variation of the fMRI voxel time course, y, in terms of a linear combination of reference functions. These reference functions can also be called predictors, regressors, covariates, or explanatory variables. Each reference function represents the expected fMRI response time course to a specific condition of the experimental paradigm, or to a confounding variable that influences the fMRI signal. The predictor time courses, X, were obtained by the convolution of a condition time course with the hemodynamic response function (HRF). Each predictor time course is associated with a certain, to be estimated, beta weight b, which represents the contribution of the predictor X to the voxel time course, y. An error term is added to account for variance in the dependent variable unexplained by the linear combination of predictors, or the model. Accordingly, the value of the voxel time course, y, at time point 1 can be formulated as\( y_1 = b_0 + b_1 X_{11} + \ldots + b_p X_{1p} + e_1 \). The first beta weight, \( b_0 \), is also known as the constant or intercept of the function. Subsequent beta weights are associated to the values of the p predictor time courses at time point 1, X, and the last term in the function represents the error term at time point 1. The value of y at all time points represents the fMRI signal. Figure 3 is adapted from Brain Voyager documentation and provides an illustration of what constitutes the GLM system of equations. For the spatial attention task, the time course of the predictor spatial attention was defined by means of convolution of the line bisection task events with the HRF. For the face recognition task, the time course of the predictor face
processing was defined by means of convolution of the face selective localizer task events with the HRF.

The GLM is most commonly presented in matrix notation, \( y = Xb + e \). The voxel time course \( y \), the beta values \( b \), and the residuals \( e \), are vectors, whereas the set of predictors, \( X \), is a matrix called the design matrix. The design matrix contains the predictor time courses as vectors. The GLM fitting procedure operates by finding a set of beta weights \( b \) explaining the data as good as possible, given the data \( y \) and design matrix \( X \). A prediction of the time course values is provided by the GLM, \( \hat{y} = Xb \). When the model provides a good fit, beta values lead to a prediction which is as close as possible to the measured values \( y \). Accordingly, the residuals \( e \), or error values, should be as small as possible. The GLM procedure estimates beta values by minimizing the sum of squared error values, as the errors can be both positive and negative. The desired beta weights minimizing the residuals are called the least squares estimates, and are obtained by \( b = (X'X)^{-1}X'y \). The \( X'X \) matrix-matrix multiplication results into the predictor variance-covariance matrix. The \( X'y \) matrix-vector multiplication results into a vector representing the elements of covariance of the predictor time course with the voxel time course. Accordingly, the variance of the voxel time course should be explained by the model as much as possible and as little as possible by the error term. Minimizing the error variance by means of least squares corresponds to maximizing the variance explained by the model, and the correlation coefficient \( R^2 = \frac{\text{Var}(\hat{y})}{\text{Var}(y)} \) is an appropriate measure of variance of the data explained by the GLM.

To test whether the model significantly explains the variance of the voxel time course, the correlation coefficient can be transformed into an F statistic \( F_{n-1,n-p} = \frac{(R^2(n-p))}{(1-R^2)(p-1)} \), with \( p \) being the number of predictors. However, to test whether not only the model in its whole, but differences in specific conditions within the model significantly explain a voxel’s time course, contrasts need to be employed. A contrast can be defined by a linear combination that is the scalar product of a contrast vector \( c \) and beta vector \( b \). The null hypothesis to be tested, stating that there are no differences between conditions of interest, can then be described as \( c'b = 0 \). For spatial attention, contrasts were defined by the line bisection performance vs. control task performance. For face processing, contrasts were defined by face stimuli block performance vs. object
stimuli block performance. In the current study, we inquired solely into the positive valued outcomes of these contrasts. More specifically, the activity difference of interest concerned higher activity for the task performance of spatial attention and face processing. A t statistic \( t = (e'b) / (\sqrt{(\text{Var}(e)c'(X'X)^{-1}c)}) \) with \( n-p \) degrees of freedom will test the significance of this contrast for all predictors. The denominator of this t statistic defines the standard error of \( e'b \), being the variability of the estimate due to noise. This t value can be converted into an error probability value \( P \), which in its turn may support the rejection of the null hypothesis if it is sufficiently small. The regular significance threshold \( \alpha \) of \( P < 0.05 \) is unadvisable in the context of fMRI research since a large amount of significance tests are employed. This is referred to as the multiple comparisons problem. A high prevalence of type I errors, or false rejections of the null hypothesis, is associated with the great amount of voxels to be tested. Therefore, corrections to the significance threshold, or type I error rate \( \alpha \), need to be made. False discovery rate (FDR) controlling procedures are suitable to obtain this correction since they control for the expected proportion of type I errors while still maintaining high power and therefore avoiding type II errors. Another option concerns the adjustment of the \( \alpha \) level from 0.05 to 0.001 without any further correction.

For the purpose of the current study, it was interesting to focus on certain Regions of Interest (ROI) in the brain. As mentioned previously, spatial attention and face recognition are characterized by their lateralized dominance in functionality in the brain. More specifically, multiple studies suggest that brain areas primarily involved in spatial attention are the intra-parietal sulcus (IPS) and the lateral peristriate cortex (LPS). Brain regions primarily involved in face processing, on the other hand, are the fusiform face area (FFA), the occipital face area (OFA) and the superior temporal sulcus (STS). When researching the difference in functional lateralization in individuals with a mirrored visceral anatomy compared to normal individuals, it may therefore be most informative to uncover whether the brain networks of spatial attention and face recognition have their functional epicentre in these lateralized ROI as well. Another advantage of a ROI approach is the fact that it minimizes the multiple comparisons problem. By limiting statistical analysis to a smaller, well-defined ROI, the number of voxels submitted to significance testing is substantially lower. Therefore, the potential amount of false positives, or invalid null hypothesis rejections, is minimized as well. In
the current study researched ROIs containing about 90000 voxels combined for each function in each hemisphere. A problem often encountered in ROI analysis is the double dipping problem, which refers to the self-confirming statistical malpractice of selecting a region of interest based on data reflecting activation in a certain task, and subsequently running statistical analyses on the same data in this ROI. To avoid the double dipping problem, ROI were defined by means of the previously described literature concerning the lateralized functional brain network of spatial attention and face processing. The ROIs for spatial attention were selected based on the study of Çicek et al. (2009). They identified The IPS and the LPS in Talairach space coordinates in the right hemisphere based on conjunction analysis. Coordinates for the IPS and the LPS in the left hemisphere were derived by mirroring the RH coordinates. The ROIs for face processing were selected based on the study of Fox et al. (2009). They identified the FFA, the OFA, and the STS as the core system of face processing. Talairach coordinates of these ROIs in both the left and right hemisphere were obtained by selecting the average coordinates of peak voxels in the ROIs that responded significantly different to faces. These ROI coordinates were imported in Brain Voyager by means of a volume of interest (VOI) file during VOI/ROI analysis.

The dependent measure of interest is the Lateralization Index (LI), which is based on the outcome of the GLM for each voxel in the defined ROIs for spatial cognition and face processing. The LI is a quantification of lateralization of activation corresponding to a particular brain function. It is typically defined as (L-R)/(L+R), and in the context of the current study it will be used in its rightward direction, being (R-L)/(R+L). The right (R) and left (L) element of the LI can be defined by brain activity in two ways: the extent, and the magnitude. When focusing on the extent of lateralization of the signal, the dependent variable of interest is the number of significantly differently activated voxels during the condition of interest compared to another condition or baseline. When focusing on the magnitude of lateralization of the signal, the dependent variable of interest is the % signal change in these voxels, or the magnitude of significance of the differently activated voxels during the condition of interest compared to another condition or baseline. Both measures of the LI can produce substantially different results, for example in case a large amount of voxels has different activity that only just reaches significance compared to when a small amount of voxels has different
activity that is largely significant. On account of providing a complete representation of the information this study and the results of the GLM have to offer, both measures of the LI were considered. The extent-based LI was calculated by replacing the R and L elements in the LI formula by the number of significantly activated voxels in the selected ROIs in the right and left hemisphere respectively. The magnitude-based LI was calculated by replacing the R and L elements in the LI formula by the maximum T statistic score in the selected ROIs in the right and left hemisphere respectively. The threshold for the LI to be considered reflecting a substantially lateralized cognitive function, can be set according to personal preference. Seghier et al. suggest employing a threshold of 0.2 for right hemisphere dominance based on extent.

Given the fact that there is high interindividual variability between the subjects concerning age, educational background, sex, and handedness, a group analysis alone would not provide clear and reliable results. Rather, subjects were mainly analyzed by means of pair wise comparison of the SI participants compared to their matched controls.

RESULTS

Face Processing

The number of voxels for each participant in the face processing ROIs in each hemisphere displaying a significant effect of the dynamic face localizer task is displayed in Table 1. In these voxels, the BOLD response during face stimuli blocks was significantly greater than the BOLD response during object stimuli blocks, \( t(154), q < 0.05 \) (FDR). The maximum t statistic value of the selected voxels is displayed alongside the amount of voxels. The maximum t value provides information about the magnitude of the effect, whereas the amount of voxels reaching significance provides information about the extent of the effect. As can be illustrated by comparing SS3 LH to SS4 LH, a high maximum t value does not necessarily imply an equally high number of voxels reaching significance, and vice versa. The total number of voxels in the face processing unihemispheric ROIs together was 85356, providing a reference to which the number of voxels reaching significance can be compared. Based on these values, the lateralization index (LI) was calculated. Table 2 displays the LIs based on the extent of
activation and the LIs based on the magnitude on activation. Figure 4 graphically displays the extent-based LIs for all SI and SS participants.

**Table 1.** Number of Voxels reaching Significance in the Dynamic Face Localizer Task and Associated Maximum t Values. t(154), q < 0.05 (FDR).

<table>
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<th>Subject</th>
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<th>Situs Inversus</th>
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<td>15159 6,78</td>
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<td>4</td>
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<td>16858 8,42</td>
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<td>2573 5,54</td>
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<td>2787 5,15</td>
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<td></td>
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<tr>
<td>13</td>
<td>R</td>
<td>131 3,43</td>
<td>385 3,80</td>
<td>311 4,26</td>
<td>1978 5,68</td>
<td></td>
<td></td>
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<tr>
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<td>4977 6,94</td>
<td>1711 5,43</td>
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<td></td>
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<tr>
<td>16</td>
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<td>4185 4,47</td>
<td>2104 4,91</td>
<td>1 3,68</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Table 2.** Extent-Based and Magnitude-Based Lateralization Index (LI) for Face Processing in Individuals with SI and SS.

<table>
<thead>
<tr>
<th>Subject</th>
<th>LI extent</th>
<th>LI magnitude</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>SS SI</td>
<td>SS SI</td>
</tr>
<tr>
<td>3</td>
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<td>-0,13 0,12</td>
</tr>
<tr>
<td>4</td>
<td>0,09 0,59</td>
<td>0,22 0,25</td>
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<tr>
<td>5</td>
<td>0,79 1,00</td>
<td>0,03</td>
</tr>
<tr>
<td>6</td>
<td>1,00 0,59</td>
<td>0,03</td>
</tr>
<tr>
<td>7</td>
<td>0,12 0,46</td>
<td>-0,07 0,01</td>
</tr>
<tr>
<td>8</td>
<td>1,00 0,07</td>
<td>0,21 -0,08</td>
</tr>
<tr>
<td>9</td>
<td>0,49 0,73</td>
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</tr>
<tr>
<td>11</td>
<td>0,50 0,73</td>
<td>0,08 0,04</td>
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<tr>
<td>13</td>
<td>1,00 -0,12</td>
<td>0,24 -0,06</td>
</tr>
<tr>
<td>14</td>
<td>0,51 0,05</td>
<td>0,05 0,00</td>
</tr>
<tr>
<td>15</td>
<td>-0,19 -0,49</td>
<td>-0,05 -0,12</td>
</tr>
<tr>
<td>16</td>
<td>-0,37 -1,00</td>
<td>-0,13 -0,14</td>
</tr>
<tr>
<td>AVG</td>
<td>0,44 0,24</td>
<td>0,05 0,02</td>
</tr>
<tr>
<td>SD</td>
<td>0,46 0,57</td>
<td>0,13 0,12</td>
</tr>
</tbody>
</table>
SS3 and SI3 both have a right hemispheric dominance for face processing according to the extent-based LI (LI > 0.2), although the rightward LI of SS3 is more outspoken. When the LI is based on magnitude, however, SS3 seems to display a more left than right hemispheric dominance for face processing, whereas the magnitude-based LI of SI3 confirms RH dominance. A potential explanation for the unusual leftward magnitude-based LI of SS3 could be an overall irregular functional lateralization. Accordingly, the participant is left handed, which is rather uncommon as well and is often associated with irregular lateralization. However, the extent-based LI of SS3 corresponds to RH dominance and it is unclear whether the extent or magnitude of activation prevails in functional lateralization. The extent-based LIs for SS3 and SI3 are in accordance with the hypothesis stating that functional lateralization of face processing will be less RH dominant in individuals with SI, whereas the magnitude-based LIs are not in accordance with this hypothesis.

The extent-based LI of SS4 is rather weak and does not correspond to LH nor RH dominance in face processing. For SI4, on the other hand, the extent-based LI corresponds to RH dominance (LI > 0.5). The magnitude-based LIs for SS4 and SI4 are both directed rightward. Both the extent- and the magnitude-based LIs for SS4 and SI4 are not in accordance with the hypothesis stating that the hemispheric specialization of
face processing is more LH dominant in SI. Again, this irregular functional lateralization of face processing might be related to other irregular functional specialization, as SS4 and SI4 are both left handed.

SS5 shows a strong RH dominance in face processing according to the extent-based LI (LI > 0.7). The extent-based LI of SI5 corresponds to an even stronger RH dominance, however, as can be found in Table 1, this is due to the 0 voxels reaching significance in the LH. There are 466 voxels reaching significance in the RH, and compared to 0, they unworthily give rise to a LI as extreme as 1. Therefore, this LI should be interpreted with caution. The extent-based LIs of SS5 and SI5 are not necessarily conflicting with, nor are they in accordance with the hypothesis stating that there will be a lower prevalence of RH dominance of face processing in SI. The LI of SS5 is highly RH dominant and is based on extensive activation of voxels in both hemispheres. The extent-based LI of SI5, however, may be highly RH dominant as well, but is based on a moderate amount of voxels reaching significance exclusively in the RH. The magnitude-based LI of SS5 is weakly rightward and no magnitude-based LI can be inferred for SI5 since the maximum t value is based only on voxels that reach significance.

The LI of SS6 should not be interpreted as being meaningful, since it is based solely on the activity of one voxel reaching significance in the RH. The extent-based LI of SI6 suggests a RH dominance in face processing (LI > 0.5) and the magnitude-based LI of SI6 is rather weak but in accordance with RH dominance. Unfortunately, no meaningful comparison of SS and SI can be made here.

The extent-based LI of SS11 and SI11 both correspond to RH dominance in face processing. In contrast to the hypothesis stating that face processing should be less RH dominant in SI, however, the LI is greater for SI11 (LI > 0.7) than for SS11 (LI > 0.5). Nevertheless, the magnitude-based LI for SS11 is more outspokenly rightward than the magnitude-based LI of SI11. SS7 compared to SI7, and SS9 compared to SI9 provide clear cases of conflict with the hypothesis stating that hemispheric specialization of face processing will be more irregular, and left hemispheric, in SI. The extent-based LI of SS7 does not correspond to dominance of any hemisphere, whereas the extent-based LI of SI7 suggests RH dominance (LI > 0.2). Moreover, although both weak, the
magnitude-based LI of SS7 is directed leftwards, whereas the magnitude-based LI of SI7 is directed rightwards. Both the extent-based LI of SS9 and SI9 correspond to RH dominance in face processing. However, the LI of SI9 (LI > 0.7) is stronger than the LI of SS9 (LI > 0.2). A similar statement can be made for the magnitude-based LIs of SS9 and SI9. These are both rightward, with the LI of SI9 being more outspoken.

The cases of SS8 compared to SI8, SS13 compared to SI13, and SS14 compared to SI14, all provide evidence in accordance with the hypothesis stating that SI coincides with an irregular, or less right hemispheric, specialization of face processing. Moreover, the case of left handed participants SS14 and SI14 suggests that atypical specialization of one function, does not necessarily coincide with atypical lateralization of another function. The extent-based LI of SS8 suggests that the RH is highly dominant in face processing (LI > 0.7), whereas the LI of SI8 does not correspond to any hemispheric dominance. The magnitude-based LI confirms this pattern by suggesting a rightward dominance in SS8 and a weak leftward dominance in SI8. The extent-based LI of SS13 corresponds to strong RH dominance in face processing (LI > 0.7), which is in correspondence with the rightward magnitude-based LI. On the contrary, the extent-based LI of SI13 does not correspond to any hemispheric dominance, and the magnitude-based LI is directed leftwards. SS14 shows RH dominance in face processing according to the extent-based LI (LI > 0.5), and the rightward magnitude-based LI. SI14 does not show any hemispheric dominance in face processing based on either LIs, as they are both too weak.

The cases of SS15 compared to SI15, and SS16 compared to SI16, provide evidence in accordance with the hypothesis as well, although the SS individuals also differ from regular functional lateralization. The extent-based LI of SS15 is nearly sufficient to correspond to LH dominance in face processing (|LI| ≈ 0.2), whereas the extent-based LI of SI15 corresponds to clear LH dominance (|LI| ≈ 0.5). The magnitude-based LIs confirm this trend, both being leftward, but stronger for SI15. The extent-based LI of SS16 also corresponds to LH dominance in face processing (|LI| > 0.2), and the extent-based LI of SI16 suggests strong LH dominance (|LI| > 0.7). Again, the magnitude-based LIs confirm this trend, both being leftward, yet stronger for SI16.
Group statistics of the total SS group compared to the SI group provide little useful information. As can be seen in Table 2, the average extent-based LI of individuals with SI is weaker than the average LI of control subjects, although both suggest RH dominance in face processing (LI > 0.2). This is in accordance with the hypothesis stating that lateralization of face processing is more irregular, and therefore less strongly RH, in individuals with SI. However, there is high interindividual variability in both groups, as the standard deviation in Table 2 indicates. A paired t test indicates that the mean extent-based LI of SS individuals is not significantly greater than the mean extent-based LI of SI individuals, \( t(11) = 1.35, P > 0.05 \). The average magnitude-based LI of individuals with SI is weaker than the average LI of control subjects as well. However, the standard deviation is large and a paired t test indicates once more that the difference between the two groups is not statistically significant, \( t(11) = 0.56, P > 0.05 \).

**Spatial Cognition**

Table 3 displays the number of voxels in the spatial cognition ROIs with a significantly greater BOLD response during the Landmark task compared to the control task for each individual and hemisphere, \( t(176) \). The total number of voxels in the unihemispheric ROIs together was 93283, providing a reference to which the number of voxels reaching significance can be compared. Under normal circumstances, this significance is thresholded by \( q < 0.05 \) (FDR). However, in many cases this threshold was too strict for the Landmark task to elicit any significantly activated voxels. This problem can result in a floor effect, which masks any differences in activation below the threshold and therefore conceals information about the lateralization of spatial attention. Nevertheless, a mild threshold would result in an increase of type I errors. Consequently, opting for the slightly less strict uncorrected threshold of \( P < 0.001 \) can provide an adequate solution for some of the 0 values. The values marked in grey have been calculated using this alternative threshold, \( t(176), P < 0.001 \). Even so, some 0 values remain. It is important to note that, once the significance threshold was adjusted for the ROI voxels in one hemisphere, this was adjusted for the ROI voxels in the other hemisphere as well in order to assure a comparable nature for the calculation of the LI. The maximum t values of the voxels reaching significance for all subjects and both
hemispheres are displayed in Table 3 as well, in order to assess the magnitude-based LI. The extent- and magnitude-based LIs for spatial cognition are displayed in Table 4. Figure 5 graphically displays the extent-based LIs for all SI and SS participants.

Table 3. **Number of Voxels reaching Significance in the Landmark Task and Associated Maximum t Values.** $t(176), q < 0.05 \text{ (FDR), } P < 0.001$.

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<th>Subject</th>
<th>Handedness</th>
<th>Situs Solitus</th>
<th>RH</th>
<th>Max T</th>
<th>LH</th>
<th>Max T</th>
<th>RH</th>
<th>Max T</th>
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</tbody>
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Table 4. **Extent-Based and Magnitude-Based Lateralization Index (LI) for Spatial Cognition in Individuals with SI and SS.**

<table>
<thead>
<tr>
<th>Subject</th>
<th>LI extent</th>
<th>LI magnitude</th>
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<td></td>
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<tr>
<td>5</td>
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<td>0.70</td>
<td>-0.08</td>
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<tr>
<td>8</td>
<td>0.71</td>
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</tr>
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</tr>
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<td>1.00</td>
<td>0.00</td>
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<tr>
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<td>0.00</td>
</tr>
<tr>
<td>16</td>
<td>-0.22</td>
<td>-1.00</td>
</tr>
</tbody>
</table>

| AVG     | 0.49      | 0.00         | 0.06      | 0.00      |
| SD      | 0.43      | 0.67         | 0.10      | 0.07      |
Figure 5. Extent-based LIs for Spatial Cognition in all Subjects. A $LI > 0.2$ indicates RH dominance and a $LI < -0.2$ indicates LH dominance.

Due to voxels not exhibiting a BOLD response reaching significance, it is impossible to compare the lateralization of spatial attention in individuals with SI and control individuals in certain cases. The resulting 0 value may seem to represent balanced lateralization, yet, no such conclusions should be drawn. For example, should the BOLD response in the voxels not reaching significance be weak in the left hemisphere and extremely weak in the right hemisphere, there is still unbalanced lateralization, albeit non-significant. No conclusions concerning the hypothesis stating that hemispheric specialization is more irregular in individuals with SI compared to control individuals should be drawn for these cases. The extent-based LI of SI6 corresponds to RH dominance in spatial attention ($LI > 0.5$). However, there is no way to infer from this LI whether the matched control of SI6, SS6, has more or less RH dominance in spatial processing. Similarly, the extent-based LI of SS15 corresponds to RH dominance in spatial attention ($LI > 0.5$), but no conclusions can be drawn from the LI of SI15. The LIs of SS13 and SI14 are both 0 values, whereas the LIs of SI13 and SS14 are -1 and 1, respectively indicating LH and RH dominance in spatial attention. However, no strong conclusions should be drawn from the size of these extreme LIs, since they are based on a comparison to 0 and are therefore easily as extreme as $|1|$.
There are a number of cases providing support for the hypothesis stating that spatial cognition will have more atypical, less RH dominance in individuals with SI compared to matched controls. SS3 (LI > 0.7), SS4 (LI > 0.5), SS7 (LI > 0.5), and SS9 (LI > 0.5) all demonstrate strong RH dominance in spatial cognition according to the extent-based LI. The extent-based LI of SI3 also corresponds to RH dominance (LI > 0.2), but with a much weaker extent than the normal control. SI4, SI7, and SI9 (|LI| > 0.7) have an extent-based LI leaning slightly leftward or indicating LH dominance. All the magnitude-based LIs of these participants confirm these trends. An interesting remark to be made here is that participants SS3, SI3, SS4, and SI4, are left handed. These findings thus suggest that atypical functional lateralization of one cognitive function does not necessarily imply atypical functional lateralization of another.

The cases of SS5 compared to SI5, and SS16 compared to SI16 provide support for the hypothesis as well. The extent-based LIs of both SS5 and SI5 suggest strong RH dominance in spatial attention (LI > 0.7). However, the LI of SI5 is less strong. The extent-based LI of both SS16 and SI16 correspond to LH dominance in spatial attention (|LI| > 0.2). However, the LI of SI6 is stronger. Nonetheless, it is most important to note that the extent-based LIs of SS5 and SI16 are based on a comparison to 0, and should therefore be interpreted with caution. This is especially the case for SI16, since there are merely 2 voxels reaching significance in the LH.

The results of this study also provide evidence contradicting the hypothesis stating that RH dominance in spatial cognition will be less prominent in individuals with SI compared to matched controls. The extent-based LI of SS11 is too weak to reach significance, whereas the LI of SI11 corresponds to RH dominance (LI > 0.2). The magnitude-based LI of SS11 is even directed slightly leftward, contrary to the rightward directed magnitude-based LI of SI11. Both the extent-based LI of SS8 and SI8 indicate RH dominance in spatial attention. The LI of SI8 is stronger and can therefore be interpreted as more RH dominant. However, this LI is based on the activation of merely 6 voxels compared to 0, and strong interpretations should therefore be avoided here once more. No comparison is possible for the magnitude-based LIs of SS8 and SI8.
Group statistics can be applied to examine whether there is a significant difference in lateralization of spatial attention between the SS and SI groups as a whole. As can be inferred from Table 4, the mean extent-based LI for spatial cognition in SS individuals suggests RH dominance (LI ≈ 0.5), whereas the mean LI in SI individuals does not correspond to LH or RH dominance. However, the standard deviation is quite high in these groups for spatial cognition as well, and it may prove interesting to examine whether this group difference is statistically significant. A paired t test revealed that the LI for spatial attention is significantly more RH dominant in SS subjects compared to SI subjects, t(11) = 2.81, P < 0.05. This result supports the hypothesis stating that spatial cognition is more atypical in lateralization, and therefore less RH dominant, in individuals with SI compared to matched controls. The mean magnitude-based LI for spatial cognition in SS individuals was directed rightward, just as the mean LI in SI individuals. However, the mean magnitude-based LI in SI subjects is weaker. The standard deviation is quite high here once more, and a paired t test revealed that the difference between the two mean magnitude-based LIs is non-significant, t(4) = 1.68, P > 0.05. The number of degrees of freedom in this t test was only 4 since there are only 5 pairs of subjects which had a comparable magnitude-based LI.

**DISCUSSION**

The results of the current study provide mixed evidence concerning the role of an inverse anatomical lateralization of visceral organs, and possibly brain anatomy, in the lateralization of two typically RH dominant brain functions, face processing and spatial cognition. In the majority of individuals with SI, the lateralization of either face processing or spatial cognition was rather atypical compared to the more RH lateralization in their matched controls. Yet, there was still a large amount of individuals with SI displaying typical RH dominance in face processing and/or spatial cognition. Moreover, some SI subjects had strong RH dominance in face processing or spatial cognition whereas their matched controls displayed an atypical lateralization. Considering the notion that lateralization of anatomy would cause lateralization of functionality in the brain, this outcome may seem somewhat implausible. However, there are many more factors to take into account when considering the role of structure-function relationships in hemispheric specialization. Moreover, this study assured
participants with a mirrored position of visceral organs, but not necessarily a mirrored position of the brain, which is an added factor of variability that should be taken into account. A mixed outcome can still provide us with useful information and directions for further research if we take into account that these mixed results are not neutral, yet interpret them with caution where necessary.

Relativity of the LI and considerations concerning the ROI

Firstly, as stated by previous literature and confirmed by the results in the current study, lateralization of a cognitive function is never a matter of complete independence or dependence upon one hemisphere. Face processing and spatial cognition are functions that rely on the functioning of a large neural network. A more realistic notion is the specialization of one hemisphere in a particular cognitive function or dominant involvement of one hemisphere over the other in a particular cognitive function. The LIs based on activation in ROIs in both hemispheres during task execution of face processing and spatial cognition indicated this hemispheric specialization by means of a proportion of voxels displaying a significant difference in BOLD response. As demonstrated, these LIs were not a matter of -1 for absolute LH dominance or 1 for absolute RH dominance, but rather a value between -1 and 1 indicating a relative dominance. Whenever an extreme value such as 1 was reported, this was the result of a comparison to 0 values, indicating a floor effect. This suggests that the found effect of laterality of anatomy on laterality of functionality is a relative matter, shifting dominance in the direction of one hemisphere to the other, rather than shifting complete determination of a function by one hemisphere to the other.

Moreover, especially for spatial cognition, several 0 values were reported in the current study. These 0 values are caused by activation, or BOLD response, in the voxels of the ROIs not reaching significance. When a LI was calculated based upon these 0 values, it was misleading. Firstly, if any amount voxels in the ROIs in one hemisphere does reach significance while no voxels in the ROIs of the other hemisphere did, the LI was more extreme than it should have been. Secondly, if no voxels in the ROIs in both hemispheres reached significance, the LI was 0 and may have seemed to reflect perfectly balanced dominance of the RH and LH, while there is no way of knowing whether this was the case. These issues raise the question as to whether the ROIs were
appropriate. More specifically, perhaps the selected face processing and spatial cognition ROIs did not adequately suit the location of activation in the brain during the execution of the face processing and spatial cognition tasks in this particular study and in these particular participants. The selected ROIs for both face processing and spatial cognition were selected based on the most robustly associated regions in previous meta-analyses, and studies on lesioned and normal subjects. Concerning face processing, having misidentified ROIs would be surprising since the coordinates of the ROIs in the current study were defined based on the execution of exactly the same task in a different study, the Dynamic Face Localizer (Fox et al., 2009). Moreover, the method used to identify the voxels for the coordinates of the ROIs was to identify the peak significantly responding voxels, which is comparable to the methods used in the current study in order to identify the LI. Fortunately, the amount of 0 values for face processing was very limited.

With regard to spatial cognition, however, there was a high amount of 0 values. It is possible that the cause for this can be found within the methodology. The coordinates of the ROIs for spatial cognition were defined based on a conjunction analysis of both a Landmark and Line Bisection task (Çicek et al., 2009). In the current study, however, only the Landmark task was employed and the measure of interest, the LI, was calculated based solely on the extent and magnitude of significantly responding voxels, without conjunction analysis with any other information. Because the emphasis of both approaches was somewhat different, some relevant information may have been overlooked. Many of the LIs of certain SS or SI participants were uninterpretable and this made a direct comparison of matched participants impossible. Perhaps these cases could have provided more evidence in favour of the hypothesis stating that structure influences function in terms of lateralization of spatial cognition. It would be advisable for future research to secure robust ROIs for robustly lateralized brain functions, and to identify clear sub-functions of those cognitive functions by selecting one specific task to be employed. Accordingly, there will be less variation in variables other than the interindividual differences in lateralization.
Ontogenetic origins of hemispheric specialization

Reverting to the theoretic framework delineating phylogenetic and ontogenetic origins, conclusions can be drawn concerning what most plausibly predominates hemispheric specialization based on the results of the current study. Starting from a smaller and moving on to a larger scale, the ontogenetic considerations will be discussed before the phylogenetic considerations. Situs inversus is a term given to a phenotype that is characterized by a mirrored position of visceral organs. However, as discussed in the introduction, this phenotype can be the result of multiple mechanisms. A first and important influencing mechanism that was introduced is natural variation of genotype in the population. If a healthy individual has a mirrored anatomical laterality due to natural disposition of genotype, it is very plausible that the genes coding for this laterality of anatomy also have an effect on the laterality of functionality in the brain. Therefore, any differences in hemispheric specialization in these individuals compared to the typical pattern may not directly be caused by brain anatomy, but would rather coincide with it or be caused by the same mechanisms. Nevertheless, anatomic asymmetry could still be an adequate predictor for hemispheric specialization, leaving its pragmatic use intact. In the current study, laterality of anatomy of visceral organs and plausibly the brain was a good predictor of the direction of hemispheric specialization in most cases. Depending on whether an individual had a normal position of visceral organs, SS, or whether an individual had a mirrored position of visceral organs, SI, the laterality of face processing and spatial cognition was more RH dominant or less RH dominant/more LH dominant, respectively. This was especially evident for spatial cognition, where the group differences were statistically significant. Hence, an individual’s anatomy can provide useful information about an individual’s functionality, albeit without a guarantee of 100% accurate prediction. For example, if an individual has suffered from a right hemispherical lesion, it will be more likely that the individual’s spatial cognition remains intact when the individual’s anatomy is more atypically lateralized and therefore not as dominantly relying on the RH.

We can take this line of thought a step further, interpreting lateralization of anatomy as a direct cause for lateralization of functionality. As mentioned in the introduction, brain structure undoubtedly influences brain function. Several participants
in the current study have Kartagener syndrome. Given the fact that this condition most plausibly corresponds to an alteration of anatomy without an alteration of underlying general genetic disposition, any difference in functional lateralization would most probably be caused by this atypical anatomy. Even when an individual does not have PCD, but has a natural genetic disposition for a mirrored anatomy, this anatomy may still have a direct effect on functionality on its own, aside from the effect of the general genetic disposition on both anatomy and functionality. Confounding factors such as age, sex, education and handedness were kept constant between matched participants in order to assure that anatomic lateralization was as close to a clean experimental manipulation as possible. When characterizing the less RH or more LH dominant LIs for face processing and spatial cognition of the SI participants as the direct result of a mirrored anatomy, certain inferences can be made. This would suggest that SI individuals in this study that display atypical hemispheric dominance for face processing or spatial cognition compared to matched controls would do so because function is inherently bonded to structure and its lateralization. This direct causal structure-function relationship suggests that by changing the laterality of anatomy of an individual’s brain, it may be possible to change its hemispheric dominance, specialization or brain function. However, this inference is only valid if SI implies mirrored anatomy of the brain as well as visceral organs. Many pairs of subjects in this study provide evidence in accordance with this idea. In contrast, there are some SI individuals who display a strongly typical lateralization of face processing and spatial cognition, whereas there matched controls do not necessarily. This is very counterintuitive given the notion of direct causality in structure-function relationships. Since the anatomic lateralization of these SI individuals is atypical while the functional lateralization is typical nonetheless, this suggests independence of hemispheric specialization from anatomic laterality. Moreover, it may imply that even though a given brain structure might not be ideal to accommodate a given cognitive function, the function will be accommodated to this structure nevertheless if its own genetic disposition implies it to.

The most realistic explanation for the current findings would be that hemispheric specialization is influenced by a number of different factors. Accordingly, both genetic predisposition of functional lateralization and direct influence of anatomy can have an
effect on hemispheric specialization of face processing and spatial cognition. As Hillis et al. (2005) stated, “Spatial cognition is influenced by more than what can be structurally detected in the brain”. Moreover, factors such as functional pathology or environmental causes may have an effect as well. It is, however, difficult to estimate when certain factors influence hemispheric specialization enough to determine dominance. For example SI11, a clear case of an individual with Kartagener syndrome, showed stronger RH dominance in both face processing and spatial cognition than matched control SS11 did. This implies that for SI11, a difference in lateralization of anatomy exclusively did not determine hemispheric specialization. In this particular case, hemispheric specialization seemed to be more plausibly determined by genetic predisposition concerning functionality, and not by anatomy and the genetic predisposition or pathology causing SI. In contrast, SI3, a participant with symptoms associated to Kartagener syndrome, showed much weaker RH dominance for spatial cognition and face processing compared to matched control SS3. This implies that for SI3, hemispheric specialization was most determined by anatomy and its mirrored position, rather than by functional genetic predisposition.

The results of the current study suggest that laterality of anatomy seems to play an important or determining role in the development of hemispheric specialization of face processing and spatial cognition in the majority of individuals. The interpretable LIs provided evidence in favour of a causal structure-function relationship in 2/3 of the cases. However, 1/3 of the interpretable cases provided evidence conflicting with a causal structure-function relationship. In these cases, individuals with SI, compared to their matched controls, did not display a direction of hemispheric specialization that could have been caused by their structural laterality. This suggests that, even though anatomy seems to play an important role in the development of hemispheric specialization and structure-function relationships, we should most certainly not minimize the extent of the influence of alternative factors.

**Phylogenetic origins of hemispheric specialization**

On a larger scale, the current study may shed some light onto the role of phylogenesis in hemispheric specialization as well. More specifically, the current results can be interpreted in favour of the causal hypothesis or the statistical hypothesis of
development of hemispheric specialization. According to the causal hypothesis, face processing and spatial cognition are typically both right hemispheric dominant because they rely on each other, because they rely on shared resources, or because of an evolutionary remnant out of which both functions evolved. According to the statistical hypothesis, face processing and spatial cognition are typically both right hemisphere dominant without any relationship or dependence upon each other. In the current study, the laterality of face processing was in accordance with the laterality of spatial cognition in the same individual in most, but not all, of the cases. For SI4, SI7, SI9, and SS15, the laterality of dominance in face processing and spatial cognition was not identical. In all other participants with interpretable LIs however, hemispheric dominance for both functions was identical. This indicates that there may be a relationship between the directions of hemispheric specialization in face processing and spatial cognition, but that this relationship is most likely not direct nor causal. Therefore, a combination of the causal hypothesis and statistical hypothesis would be most realistic.

Comparison to previous research and Suggestions for future research

The findings of the current study are scarcely in accordance with previous studies examining individuals with SI. Matsumoto et al. (1997) stated that the incidence of right handedness versus left handedness in individuals with SI was consistent with the typical ratio in the normal population. However, in the current study 1/3 of randomly selected individuals with SI was left handed. 1/3 of the selected control subjects was, of course, left handed as well, but this was due to matching conditions. The ratio of 1/3 deviates strongly from the well-known approximation of 10% left handedness in the normal population. Therefore, compared to the study of Matsumoto et al. (1997), the current study implies a stronger relationship between the anatomic laterality of the viscera and development of behavioural and functional asymmetries. Kennedy et al. (1999) mainly inquired into the presence of anatomic brain differences in individuals with SI compared to SS, but reported an absence of functional dominance differences in the domain of language. We can conclude that the results of the current study are not in accordance with the latter finding, since there were some functional dominance differences in the domain of spatial cognition and face processing for individuals with SI, albeit mixed evidence. Nevertheless, since Kennedy et al. (1999)
examined an entirely different cognitive function, conclusions based on their study may not be comparable to conclusions in the context of the current study. Tanaka et al. (1999) found that individuals with SI did not have a reduced right ear advantage compared to matched controls and concluded that “the system that produces functional asymmetry in the human brain must independently recognize laterality from situs asymmetry”. The current study, however, contradicts this by showing that structure and functional asymmetry are not completely independent. Lastly, Ihara et al. (2010) found that 2 out of 3 individuals with SI had an atypical hemispheric dominance for language. Moreover, they showed that SI of the viscera was related to some, but not all, mirrored structural asymmetries in the brain, and that the occurrence of some structural asymmetries coincided with the direction of functional asymmetries. These findings seem to be in accordance with the findings of the current study, suggesting that structural asymmetries are related to functional asymmetries in most individuals, but not in all, indicating the added influence of alternative factors.

The strength of the current study compared to previous SI studies was its use of a much larger sample size, adequate control subjects, and a broader scope of examined lateralized cognitive functions. By inquiring into typically right hemispheric dominant cognitive functions, we were able to reveal completely new and crucial information. Firstly, the current study showed that the role of anatomy in hemispheric specialization may not be completely determinant, but should definitely not be neglected. Secondly, the results of the current study allow us to compare information from hemispheric specialization in both hemispheres, in contrast to focusing solely on typically LH dominant cognitive functions. Thirdly, the current study shed some more light onto structure-function relationships in general. On the other hand, the latter introduces an important weakness of the current study as well.

Aside from strengths, the current study also has some shortcomings. Although structural scans were carried out, the data provided by these scans were not examined further in the current study aside from their necessary involvement in functional data analysis. Any conclusions that can be drawn from the results of functional data analysis are, however, restricted by the fact that it is unknown whether the individuals with SI, aside from their viscera, have a mirrored anatomy of the brain as well. Conclusions can
be drawn about structure-function relationships and their origins in general, but a more causal relationship between the anatomy and the functioning of the brain itself is impossible to examine. Incorporating information about the anatomical lateralization of the brain in these individuals would provide a wide range of additional information. Moreover, information about the performance on the execution of the face processing and spatial cognition tasks was not included in the current study either. As De Schotten et al. (2011) implied, performance of a cognitive function can, at least to some extent, be predicted by characteristics of the functional network. Future research might benefit from examining the relationship between the direction and extent of anatomic asymmetry, hemispheric specialization, and behavioural performance concerning the cognitive functions involved. This would help identify the consequences of differences in anatomic asymmetry and hemispheric specialization, further clarifying to what extent anatomic asymmetry can be used to predict and treat functional deficits.

CONCLUSION

Based on the results of the current study, the hypothesis stating that individuals with SI should show a more atypical hemispheric specialization of face processing and spatial cognition due to their mirrored anatomy can neither completely be confirmed nor refuted. However, we can conclude that as expected, there is a higher prevalence of atypical lateralization of face processing and spatial cognition in individuals with SI compared to matched controls, with great interindividual differences. There are most probably multiple factors underlying the development of functional asymmetries, and structural asymmetry seems to be a factor that has great predictive value in most individuals. The findings of the current study provide crucial new insights that can give direction to promising future research.
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