CORTEX 106 (2018) 12–25

Available online at www.sciencedirect.com

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Journal homepage: www.elsevier.com/locate/cortex

Research report

Atypical brain functional segregation is more frequent in situs inversus totalis

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ARTICLE INFO

Article history:
Received 24 October 2017
Reviewed 22 January 2018
Revised 20 February 2018
Accepted 26 April 2018
Action editor H. Branch Coslett
Published online 16 May 2018

Keywords:
Functional segregation
Lateralization
Brain asymmetry
Situs inversus totalis
Atypical functional segregation
Reversed typical functional segregation

ABSTRACT

Most humans show typical brain functional specialization with language and praxis favoring left hemisphere lateralization and spatial attention and face recognition showing right hemisphere dominance. Lateralization of these cognitive functions was investigated using fMRI in participants with complete visceral reversal and matched control participants. While most participants revealed typical brain organization, atypical functional segregation was significantly more frequent in participants with visceral reversal. Interestingly, some left handers maintained typical functional segregation but showed complete reversal of all cognitive functions regardless of visceral organization. Cognitive performance, as measured with a neuropsychological test battery, was significantly predicted by the degree of atypical functional segregation of praxis and spatial attention. Increased deviation from typical functional segregation paired with lower cognitive performance. The findings suggest that typical functional segregation reflects an optimal evolutionary solution with deviations being associated with reduced cognitive performance.

1. Introduction[1]

Functional segregation between the two hemispheres of the brain is believed to result in more efficient neural processing. Increased efficiency through hemispheric specialization is explained in terms of conflict prevention of duplicate functional regions, enhancement of parallel processing, and higher neural capacity by eliminating redundant duplication (Levy, 1977; Vallortigara, 2000; Vallortigara, Rogers, & Bisazza, 1999). In addition to the resulting selection advantage over a symmetric brain, evolutionary pressure in humans also favors a prototypical functional differentiation as most humans have their left hemisphere dominant for language, praxis, and calculation and their right hemisphere in control of spatial attention, prosody, and face recognition. If this pattern of

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[1] Abbreviations used in this article: AFS (atypical functional segregation), LI (lateralization index), PCD (primary ciliary dyskinesia), rTFS (reversed typical functional segregation), SI (situs inversus), SIT (situs inversus totalis), TFS (typical functional segregation).

https://doi.org/10.1016/j.cortex.2018.04.012
0010-9452/

hemispheric specialization also reflects optimal functional segregation, then typical brain organization could be associated with better cognitive performance. Several studies have addressed this question by investigating the relation between hemispheric lateralization and cognitive performance but report contradictory results. Some studies claim significant lateralization/performance correlations (Boles, Barth, & Merrill, 2008; Mellet, Zago, et al., 2014) but only in those with a consistent hand preference (Chiarello, Vazquez, Felton, & Leonard, 2013) or when lateralization was moderate but not when strong (Hirnstein, Leask, Rose, & Hausmann, 2010), while other studies reveal no relation (Lust, Geuze, Groothuis, & Bouma, 2011; Lust, Geuze, Groothuis, van der Zwan, et al., 2011), and still others report a negative correlation between lateralization strength and cognitive performance (Boles et al., 2008; Hirnstein, Hausmann, & Gunturkun, 2008; Ladavas & Umilta, 1983; O'Boyle et al., 2005).

We investigated hemispheric lateralization of several cognitive functions in participants with atypical lateralization of visceral organs, a condition called situs inversus (SI). Individuals with SI exhibit either a complete reversal of thoracic and abdominal organs (situs inversus totalis, SIT) or a partial reversal of some internal organs (situs ambiguus). The prevalence of situs inversus in adults is estimated to be 1 in 10,000 (Rott, 1979; Torgersen, 1950). Although the exact origin and mechanics of visceral asymmetry remain a matter of debate (Vandenberg & Levin, 2010), the few published studies of brain asymmetries in individuals with SIT have reported reversed structural brain asymmetries (Ihara et al., 2010; Kennedy et al., 1999; Schuler et al., 2017; Tubbs, Wellons, Salter, Blount, & Oakes, 2003) suggesting a possible relation between visceral and neural asymmetries that was also noted in animals (Bisgrove, Essner, & Yost, 2000; Goto et al., 2010; Long, Ahmad, & Rebagliati, 2003; Wehrmaker, 1969). In the fsi (frequent situs inversus) line of zebrafish for example, complete situs inversus of viscera and brain structures was associated with reversal of two typical behaviors (mirror viewing and approaching a target to bite) whereas other behaviors (associated with swimming from a dark chamber in a new environment) were not (Barth et al., 2005). In humans, reports on language lateralization in SIT in general revealed typical left hemisphere dominance (Kennedy et al., 1999; Schuler et al., 2017; Tanaka, Kanzaki, Yoshibayashi, Kamiya, & Sugishita, 1999), but groups are very small and one study reported right hemisphere language dominance in two out of three participants with SIT (Ihara et al., 2010). Recently we reported on brain structural and functional asymmetries related to language in the largest SIT cohort studied with neuroimaging thus far (Vingerhoets et al., 2018). In short, we found that SIT participants on average show reversed Yakovlevian brain torque (petalia and midline bending) but appear to have typical brain structural and functional asymmetries related to language.

The present study investigates the relation between more general brain organization and cognition in the same cohort of SIT and control participants. We present new behavioral and brain imaging data for 15 SIT participants and an age, sex, handedness, and education matched control cohort on cognitive performance and functional brain organization. Cognitive performance was assessed by means of a comprehensive neuropsychological test battery while brain functional organization was evaluated using four cognitive localizers that required the participants to generate words, pantomime tools, make visuospatial decisions and observe human faces. Asymmetry in brain activation measured during these tasks was taken to reflect hemispheric lateralization for language, praxis, spatial attention and face recognition respectively.

2. Materials and methods

2.1. Participants

The study was approved by the Research Ethics Committee and following institutional approval the database of Ghent University Hospital was searched for the term 'situs inversus' in radiological protocols of patients aged 18–70 years. By using the contact information available, these individuals were sent information describing the rationale and protocol for the study and invited to participate. Written informed consent was obtained according to the Declaration of Helsinki. A similar procedure was applied at Middelheim Hospital, Antwerp. Seventeen participants suspected to have SI (SI01 through SI17) agreed to take part and, after informed consent was obtained, underwent a neuroimaging protocol described below. The participants provided written consent to access the actual radiological files that were consulted to determine the type of situs inversus and possible comorbidities. Radiological information (RX or CT) of thorax and complete abdomen was available in 9 participants, and of thorax and upper abdomen in 8 participants. The medical reports confirmed that all participants presented with radiologically documented situs inversus totalis, except SI01 who had situs ambiguus (levocardio) and SI10 whose protocol mentioned the term 'situs inversus' in a context unrelated to the visceral condition of the patient. The latter two participants were excluded from the study. The SI sample thus consisted of 15 individuals with situs inversus totalis, 7 women and 8 men that were between 18 and 50 years old.

In five participants with SIT a formal diagnosis of primary ciliary dyskinesia (PCD) or Kartagener syndrome was found in their medical records. PCD is a rare genetic disorder characterized by imperfect synthetization of the motor protein Dynein which results in hypomotility of the primary cilia (Afzelius, 1976; Kosaki & Casey, 1998; Leigh et al., 2009). Since about half of patients with PCD present with situs inversus, disturbed movement of nodal cilia during embryogenesis is believed to result in a random allocation of visceral laterality (Bush et al., 1998). After birth, defective ciliary motion leads to recurrent infections of the upper and lower respiratory tracts and subfertility in both sexes. Combination of situs inversus, chronic sinusitis, and bronchiectasis is known as Kartagener syndrome. However, only 20–25% of individuals with SI have PCD which indicates that causal mechanisms of SI other than chronic PCD must exist (Rott, 1979), an observation which is in agreement with alternative suggestions on the origin of symmetry breaking (Vandenberg & Levin, 2013). All five PCD-