EXPOSÉ

"Sex Differences in Acute Visuospatial Neglect – An Exploratory Study Investigating Differences in Lesion Patterns and Disconnectome"

Tamara Keßler
- Graduate School of Neural & Behavioural Science -
Master Thesis | Division of Neuropsychology

Highlights

- Are there sex differences in visuospatial neglect-related lesion patterns and/or disconnectivities?
- Differences in hemispheric asymmetry linked to differences in functional disruptions
- Interaction effect of sex and age on stroke and neglect physiology

Keywords

sex differences; visuospatial neglect; acute stroke; lesion-behaviour mapping; disconnectome

1 Introduction/State of the Art/Background

Cognition and brain health are influenced by many variables, one of them being biological sex. It has been established that healthy men typically show higher performance in spatial cognition tasks, whereas women typically score higher in memory tasks. Those sex differences cannot be (fully) explained by differences in brain structure, but rather by differences in hemispheric asymmetry and brain connectivity (Hirnstein, Hugdahl & Hausmann, 2018; Ingalhalikar et al., 2013). However, there are also important clinical implications of those sex differences, as women experience significantly more strokes than their male counterparts, and are often reported to suffer from increased stroke severity, delayed treatment, and worse recovery with decreased quality of life afterwards (Bonkhoff et al., 2021; Bushnell et al., 2018).

In the past few years, the interest in researching sex differences in stroke has increased significantly, as this step towards more personalised medicine is likely to improve stroke treatment and recovery and may even contribute to future stroke prevention (Bonkhoff et al., 2021; Bushnell et al., 2018; Hawe et al., 2020).

In a recent study, Bonkhoff et al. (2021) established that following acute ischemic strokes women and men develop different lesion patterns, which may underlie the sex-specific differences in stroke severity and functional impairments. They found that women typically presented with more spread lesion patterns, meaning that more regions contribute to stroke severity in women – even though lesion volume did not differ significantly between the sexes. Interestingly, they also observed an interaction effect of sex and age, as those sex-specific lesion pattern effects only arose after the age of 52 – the median age of menopause, which suggests that (changes in) sex hormones also affect stroke physiology and outcome (see also Bushnell et al., 2018).

It must be noted, however, that stroke is a neurological condition that can cause a number of other neuropsychological conditions, as even small focal lesions can significantly disrupt the brain network's connectivity and thus, functionality (Carrera & Tononi, 2014; Griffis et al., 2019). One syndrome that commonly occurs during the acute stage after predominantly right hemispheric lesions is visuospatial neglect (Li & Malhotra, 2015; Stone, Halligan &

Greenwood, 1993). These patients exhibit deficits in visuospatial attention in the form of a pathological spatial bias of their attentional focus towards the ipsilesional side (Karnath, 2015; Karnath & Rorden; 2012). This bias may even affect mental representations and perceptual memories (Bisiach & Luzzatti, 1978; Beschin et al., 1997). Previous research has shown that performance in some of the tests that are typically used for neglect diagnoses, such as the line bisection task[1], is influenced by both sex and age: With increasing age, performance decreases in women, while no such trend exists in men (Varnava & Halligan, 2007).

1.1 Open Questions

While sex differences in stroke physiology have received a lot more attention in research in the past few years, to the best of our knowledge, sex differences in the neural underpinnings of visuospatial neglect have not been studied so far. Therefore, it would be of interest to investigate what kind of differences can be identified in lesion patterns and disconnectivity between the sexes. Specifically, we want to investigate if we can find sex-specific lesion patterns, similar to the ones Bonkhoff et al. (2021) described. Further, we want to investigate if the sex differences in hemispheric asymmetry and brain connectivity that have been described for healthy men and women also result in sex differences in white matter disconnectivity after stroke. We aim to take an exploratory approach for this study, so we might investigate further questions that arise during the data analysis.

2 Material and Methods

2.1 Sample

We aim to re-analyse a minimum of 200 structural brain scans (equal number of men and women; both MRI and CT scans) that were acquired from patients diagnosed with visuospatial neglect during the acute stage after their stroke. In this case, we define “acute stage” as both the test for neglect being completed and the structural brain scan being acquired within 14 days after stroke. Besides the patients’ sex, their age will also be taken into account for analyses.

2.2 Statistical Analyses

The statistical analyses will be conducted using the MATLAB (MathWorks) toolboxes SPM12 (Wellcome Department of Cognitive Neurology, London), Clinical (NeuroImaging Tools & Resources Collaboratory, 2014), Clusterize (de Haan et al., 2015), Lesion Quantification Toolkit (Griffis et al., 2021) and NiiStat (NeuroImaging Tools & Resources Collaboratory, 2019). Since the data has already been acquired in the past, the majority of it has already been pre-processed in the past. Any scans that have not been pre-processed using the Clinical/Clusterize toolboxes, will be pre-processed to match the others. For quality control purposes, spatial normalisation of every scan will be checked again.

For the lesion pattern analysis, we will use a voxel-based lesion symptom mapping approach (see de Haan & Karnath, 2018 for an overview). For this, we will first cluster the patients by their lesions to then compare their behavioural performance scores (i.e., their neglect severity)

[1] Participants are presented with a line and are asked to bisect the line by marking its middle point. Healthy participants usually are relatively accurate, whereas some neglect patients show a significant rightwards bias.

between groups (male versus females). This will allow us to infer which regions contribute to sex-specific differences in symptom severity.

For the disconnectome analysis, individual white matter disconnectivity topographies will be created for every patient, which will allow us to assess the impact a given lesion has on the brain connectivity as a whole. To directly assess what kind of disconnections are involved in the typical visuospatial deficits of neglect, structural disconnectivity matrices will be created. We will first create those disconnectivity topographies and matrices on a single subject level, before calculating separate generalised linear models (GLM) for women and men and assessing if different disconnections are significantly associated with neglect symptoms/behaviour.

We want to note, however, that these planned analyses may be subjected to change during the course of the project.

3 Hypotheses

Following Bonkhoff et al. (2021), we expect to find more widespread lesion patterns in women compared to men, while we expect no significant differences in lesion volume.

Ingalhalikar et al. (2013) described that healthy women have increased interhemispheric connectivity, whereas men have stronger connectivity within the their hemispheres – or in other words: men exhibit a stronger hemispheric asymmetry. Taken together with Griffis et al.'s (2019) conclusion that interhemispheric disconnections are associated with wider spread functional disruptions, we hypothesise that, compared to males, female neglect patients' lesions cause more interhemispheric white matter disconnections, which would correlate with their increased neglect severity (see also Bonkhoff et al., 2021). Thus, we expect to find sex-specific disconnection patterns.

We think it is possible that those anticipated effects may only become significant at increased ages (Bonkhoff et al., 2021; Bushnell et al., 2018; Varnava & Halligan, 2007). Therefore, we will also investigate if we can find any difference within the groups when contrasting younger with older individuals.

4 Schedule/Work Plan

Activity	Month					
	1	2	3	4	5	6
Literature research	x					
Check exclusion criteria for every patient	x	x				
Check normalisation for every scan/patient (+ Normalise missing scans)	x	x				
Lesion pattern analysis			x	x		
Disconnection analysis			x	x		
Evaluation of analyses				x	x	
Writing					x	x

References

Beschin, N., Cocchini, G., della Sala, S., & Logie, R. H. (1997). What the Eyes Perceive, The Brain Ignores: A Case of Pure Unilateral Representational Neglect. *Cortex*, *33*(1), 3–26. https://doi.org/10.1016/s0010-9452(97)80002-0

Bisiach, E., & Luzzatti, C. (1978). Unilateral Neglect of Representational Space. *Cortex*, *14*(1), 129–133. https://doi.org/10.1016/s0010-9452(78)80016-1

Bonkhoff, A. K., Schirmer, M. D., Bretzner, M., Hong, S., Regenhardt, R. W., Brudfors, M., Donahue, K. L., Nardin, M. J., Dalca, A. V., Giese, A. K., Etherton, M. R., Hancock, B. L., Mocking, S. J. T., McIntosh, E. C., Attia, J., Benavente, O. R., Bevan, S., Cole, J. W., Donatti, A., . . . Rost, N. S. (2021). Outcome after acute ischemic stroke is linked to sex-specific lesion patterns. *Nature Communications*, *12*(1). https://doi.org/10.1038/s41467-021-23492-3

Bushnell, C. D., Chaturvedi, S., Gage, K. R., Herson, P. S., Hurn, P. D., Jiménez, M. C., Kittner, S. J., Madsen, T. E., McCullough, L. D., McDermott, M., Reeves, M. J., & Rundek, T. (2018). Sex differences in stroke: Challenges and opportunities. *Journal of Cerebral Blood Flow & Metabolism*, *38*(12), 2179–2191. https://doi.org/10.1177/0271678x18793324

Carrera, E., & Tononi, G. (2014). Diaschisis: past, present, future. Brain, 137(9), 2408–2422. https://doi.org/10.1093/brain/awu101

de Haan, B., Clas, P., Juenger, H., Wilke, M., & Karnath, H. O. (2015). Fast semi-automated lesion demarcation in stroke. *NeuroImage: Clinical*, *9*, 69–74. https://doi.org/10.1016/j.nicl.2015.06.013

de Haan, B., & Karnath, H. O. (2018). A hitchhiker's guide to lesion-behaviour mapping. Neuropsychologia, 115, 5–16. https://doi.org/10.1016/j.neuropsychologia.2017.10.021

Griffis, J. C., Metcalf, N. V., Corbetta, M., & Shulman, G. L. (2019). Structural Disconnections Explain Brain Network Dysfunction after Stroke. Cell Reports, 28(10), 2527–2540.e9. https://doi.org/10.1016/j.celrep.2019.07.100

Griffis, J. C., Metcalf, N. V., Corbetta, M., & Shulman, G. L. (2021). Lesion Quantification Toolkit: A MATLAB software tool for estimating grey matter damage and white matter disconnections in patients with focal brain lesions. *NeuroImage: Clinical*, *30*, 102639. https://doi.org/10.1016/j.nicl.2021.102639

Hawe, R. L., Cluff, T., Dowlatshahi, D., Hill, M. D., & Dukelow, S. P. (2020). Assessment of Sex Differences in Recovery of Motor and Sensory Impairments Poststroke. *Neurorehabilitation and Neural Repair*, *34*(8), 746–757. https://doi.org/10.1177/1545968320935811

Hirnstein, M., Hugdahl, K., & Hausmann, M. (2018). Cognitive sex differences and hemispheric asymmetry: A critical review of 40 years of research. *Laterality: Asymmetries of Body, Brain and Cognition*, *24*(2), 204–252. https://doi.org/10.1080/1357650x.2018.1497044

Ingalhalikar, M., Smith, A., Parker, D., Satterthwaite, T. D., Elliott, M. A., Ruparel, K., Hakonarson, H., Gur, R. E., Gur, R. C., & Verma, R. (2013). Sex differences in the structural connectome of the human brain. *Proceedings of the National Academy of Sciences*, *111*(2), 823–828. https://doi.org/10.1073/pnas.1316909110

Karnath, H. O. (2015). Spatial attention systems in spatial neglect. *Neuropsychologia*, *75*, 61–73. https://doi.org/10.1016/j.neuropsychologia.2015.05.019

Karnath, H. O., & Rorden, C. (2012). The anatomy of spatial neglect. *Neuropsychologia*, *50*(6), 1010–1017. https://doi.org/10.1016/j.neuropsychologia.2011.06.027

Li, K., & Malhotra, P. A. (2015). Spatial neglect. Practical Neurology, 15(5), 333–339. https://doi.org/10.1136/practneurol-2015-001115

Stone, S. P., Halligan, P. W., & Greenwood, R. J. (1993). The Incidence of Neglect Phenomena and Related Disorders in Patients with an Acute Right or Left Hemisphere Stroke. Age and Ageing, 22(1), 46–52. https://doi.org/10.1093/ageing/22.1.46

Varnava, A., & Halligan, P. W. (2007). Influence of Age and Sex on Line Bisection: A Study of Normal Performance with Implications for Visuospatial Neglect. Aging, Neuropsychology, and Cognition, 14(6), 571–585. https://doi.org/10.1080/13825580600826454