Thesis

submitted in partial fulfilment of the requirements for the degree

**Master of Science**

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

**Graduate School of Neural and Behavioural Sciences**

Faculty of Science  
Faculty of Medicine

Eberhard-Karls-Universität Tübingen

Presented by

Tamara Keßler,

born in Wiesbaden, Germany

Tübingen, [DATE OF SUBMISSION]

**Thesis Advisor:** Prof. Dr. Dr. Hans-Otto Karnath

Division of Neuropsychology   
 University Clinics Tübingen & Hertie Institute for Clinical Brain Research

**Second Reader:** Prof. Dr. Birgit Derntl

Department of Innovative Neuroimaging   
Center for Mental Health Tübingen

**Disclosures:**

I affirm that I have written the dissertation myself and have not used any sources and aids other than those indicated.

I affirm that I have not included data generated in one of my laboratory rotations and already presented in the respective laboratory report.

Date / Signature: \_

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Abstract

[200 words]

Cognition and brain health are influenced by many variables, one of them being biological sex.

## Introduction: Sex Differences in Neuropsychology

### Sex Differences in the Healthy Brain and General Cognition

* Varnava, Halligan & Peter (2007):
  + Hellige (2001) suggested that differences occur because the hemispheric asymmetry is not the same for males and females. This is plausible in view of the evidence that sex hormones influence cognition and brain function both at critical stages of ontogenetic development (Geschwind & Galaburda, 1987) and in adulthood as various hormonal levels fluctuate over time (Kimura & Hampson, 1994).
* Ingalhalikar et al. (2014):
  + With the advent of neuroimaging, multiple studies have found sex differences in the brain (4) that could underlie the behavioral differences. Males have larger crania, proportionate to their larger body size, and a higher percentage of white matter (WM), which contains myelinated axonal fibers, and cerebrospinal fluid (5), whereas women demonstrate a higher percentage of gray matter after correcting for intracranial volume effect (6). Sex differences in the relative size and shape of specific brain structures have also been reported (7), including the hippocampus, amygdala (8, 9), and corpus callosum (CC) (10). Furthermore, developmental differences in tissue growth suggest that there is an anatomical sex difference during maturation (11, 12), although links to observed behavioral differences have not been established.
  + Advances in fiber tractography with diffusion imaging can be used to understand complex interactions among brain regions and to compute a structural connectome (SC) (31). Similar functional connectomes (FCs) can be computed using modalities like functional MRI, magnetoencephalography, and EEG. Differences in FCs have revealed sex differences and sex-by-hemispheric interactions (32), with higher local functional connectivity in females than in males (33). Although SCs of genders have displayed small-world architecture with broad-scale characteristics (34, 35), sex differences in network efficiency have been reported (36), with women having greater overall cortical connectivity (37).
  + The myelinated axons of WM facilitate distant signal conduction. Previous data from structural imaging showed a higher proportion of cortical WM in the males, except in the CC (40, 41). A higher proportion of myelinated fibers within hemispheres in males compared with an equal or larger volume of WM in the callosum suggests that male brains are optimized for communicating within the hemispheres, whereas female brains are optimized for interhemispheric communication.

### Sex Differences in Stroke

Vascular diseases, such as stroke and ischemic heart diseases, currently constitute the second leading cause of death worldwide and are one of the leading causes of disability, especially in the elderly population ([Bonkhoff et al., 2021](#bonkhoff2021); [Feigin et al., 2014](#feigin2014); [Katan & Luft, 2018](#katanluft2018)). The Lancet’s Global Burden of Disease (GBD) review for the year 2019 reported 12.2 million global incident cases of stroke. 62.4% of those strokes were of an ischaemic nature, while the remaining 37.6% were haemorrhages. They further identified stroke to be the second-leading cause of death, accounting for a total of 6.55 million global deaths, and one of the top leading causes of long-term disabilities as measured by disease-adjusted life years (DALYs). Women suffered more often from strokes (6.44 million incident cases, 56.4 million prevalent cases) than men (5.79 million incident strokes, 45.0 million prevalent cases). However, there were no significant sex differences in the number of stroke-related deaths ([GBD 2019 Stroke Collaborators, 2021](#GBDstroke2021)).

Researchers believe that women’s higher burden of stroke may be in part due to their higher life expectancy, but also due to neurobiological differences, such as sex-specific hormones that contribute to different responses to cerebral ischemia [ok but what does that mean GURL] (Bushnell et al., 2018; Bonkhoff et al., 2021).

* Bushnell et al. (2018):
  + The incidence of human stroke is sexually dimorphic until late in life, well beyond the years of reproductive senescence and menopause. From early through midadulthood years, stroke incidence is lower in women compared to men. However, with advancing age, the incidence of stroke and stroke-related mortality becomes higher in women.1 This overarching observation has led to much work and the notion that biologic mechanisms of cell death in the ischemic brain are influenced in part, by biologic sex and in part, by the availability of female and male sex steroids before or after injury. These hormones clearly contribute to, but do not fully account for, sex-specific responses to cerebral ischemia.106
  + Biologic sex influences many variables that are important to brain health in general, and to stroke or cerebral ischemia in particular, such as general health status, cerebrovascular anatomy and function, unique risk factors such as pregnancy and preeclampsia, symptomatology, and therapeutic response.
* Bonkhoff et al. (2021):
  + Stroke affects >15 million people each year1. It is known to result in a substantial overall degree of long-term impairment across men and women2,3. However, numerous epidemiological studies indicate clinically relevant, sex-related differences in the characteristics of ischemic cerebrovascular disease4,5. For instance, due to a longer life expectancy, more women than men experience a stroke each year6.
  + women are often reported to experience higher acute stroke severity than men.
* Katan & Luft (2018):
  + The most prominent causes of death are vascular in nature, and stroke is currently the second leading cause of death worldwide.2 Ischemic heart disease and stroke together accounted for 15.2 million deaths (15–15.6 million) in 2015.2 While ischemic strokes comprise the highest number of stroke, much of the global burden of stroke measured in proportion to mortality and by mortality and disability-adjusted life-years (DALYs) is allocated to hemorrhagic stroke.3
  + Stroke is one of the leading causes of long-term disability in the United States, especially in the elderly population in which stroke incidence is highest.
  + Moreover, an increase in stroke incidence and DALYs in adults aged 20 to 64 years has been observed.
* Haast, Gustafson & Kiliaan (2012):
  + While premenopausal women experience fewer strokes than men of comparable age, stroke rates increase among postmenopausal women compared with age matched men. This postmenopausal phenomenon, in combination with living longer, are reasons for women being older at stroke onset and suffering more severe strokes.
  + Ischemic stroke accounts for 87% of all strokes, while 10% are intracerebral hemorrhage and 3% are subarachnoid hemorrhage strokes. (see also 2011 AHA Stroke Update)

### Visuospatial Neglect

Visuospatial neglect is a neurological syndrome that commonly occurs in the acute stage after predominantly right hemispheric stroke, though it may also be caused by other forms of unilateral brain injury ([Karnath & Rorden, 2012](#karnathrorden2012); [Li & Malhotra, 2015](#limalhotra2015); [Stone, Halligan & Greenwood, 1993](#stone1993)). While there’s no consensus on the exact prevalence of neglect, more conservative estimates report a prevalence of ~16% in the acute phase after stroke (e.g.: [Ten Brink et al., 2016](#tenbrink2016)), while others report a prevalence of about 30-45% (e.g.: [Bowen, McKenna & Tallis, 1999](#bowen1999); [Buxbaum et al., 2004](#buxbaum2004); [Corbetta, 2014](#corbetta)), with a few studies reporting prevalence to be as high as 82% (e.g.: [Stone, Halligan & Greenwood, 1993](#stone1993)).

Visuospatial neglect is often described as a “heterogenous collection of symptoms”. After right hemispheric lesions, neglect patients exhibit pathological spatial biases towards the ipsilesional (right) side of space. This manifests as a deviation of their eye and head position, as well as an attentional bias both at rest and during goal-directed behaviour towards the ipsilesional side. At the same time, patients have difficulties in orienting towards the contralesional side and will typically ignore stimuli and people located on that side ([Becker & Karnath, 2010](#beckerkarnath2010); [Karnath, 2015](#karnath2015); [Karnath & Rorden, 2012](#karnathrorden2012)). [MORE] [REAL LIFE EXAMPLE]

[Attentional system? Model?]

This biased behaviour becomes especially obvious when patients are asked to engage with a scene or set of stimuli, for example during visual search or while copying an image, as patients will typically omit the left half of the scene. Therefore, many clinical tests that are used for diagnosing and/or quantifying the severity of neglect employ cancellation tasks to assess the spatial extent of a patient’s visual search (see 2.2. Behavioural Data for more detail; see also Rorden, Karnath, 2010).

Often times, visuospatial neglect may affect multiple modalities and, in some cases, may even affect mental representations and perceptual memories ([Bisiach & Luzzatti, 1978](#bisiachluzzatti1978); [Beschin et al., 1997](#beschin1997)). [is this even relevant?]

On a neurological level, stroke-induced neglect most often occurs after right unilateral brain damage in the territory of the middle cerebral artery (MCA) ([Li & Malhotra, 2015](#limalhotra2015)). The perisylvian network, including the temporo-parietal junction (TPJ), inferior parietal lobule (IPL), superior and middle temporal cortex, insula and ventrolateral prefrontal cortex (vlPFC), have been implicated in contributing to the core deficits ([Karnath & Rorden, 2012](#karnathrorden2012); more sources); The white matter connections in between those areas, specifically the superior longitudinal fasciculus (SLF), the inferior occipitofrontal fasciculus (IOF) and the superior occipitofrontal fascicle (SOF) have been shown to be particularly vulnerable to causing neglect after being damaged (He et al., 2007; Karnath, Rorden & Ticini, 2009;

* 1. Motivation

## Material & Methods

### Patient Sample

This study reanalysed a subset of 222 patients from the Division of Neuropsychology’s RHLM (Right-Hemispheric Lesion ?) databank, which comprises a total of 551 right-hemispheric stroke patients. All data were acquired at the Centre of Neurology at the University Clinic of Tübingen between January 2000 and February 2021. The patient data had been used for previous studies conducted at the Division for Neuropsychology at the University Clinic of Tübingen. All patients provided their informed consent for study participation and scientific data usage. The study was conducted in accordance with the revised guidelines from the Declaration of Helsinki.

The exclusion criteria for the study were as follows:

* Imaging data must have been acquired during the acute phase after the patient’s stroke, i.e., within 14 days
* The imaging data revealed a demarcated lesion
* The patient experienced no previous strokes, traumatic insults, or brain tumours
* The patient completed at least two out of the three diagnostic tests for visuospatial neglect during the acute phase after the patient’s stroke, i.e., within 14 days
  + If only two of the three tests were completed, their results must be sufficient for a clear diagnosis, i.e., the patient must exhibit clear symptoms/a lack of symptoms indicative of neglect in both tests

Following these criteria, a total of 329 patients had to be excluded. 124 patients were excluded due to missing data, 57 for medical counterindications, 55 for exceeding the 14-day threshold of the acute stroke phase, [man] and two patients were excluded as no clear diagnosis was possible based on their diagnostic test scores. Additionally, 40 patients had to be excluded due to the poor quality of their (normalised) brain scans.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Total  (N = 222) | Female  (N = 103) | Male  (N = 119) | p-value |
| Age *(years)* | 62.6 (13.8) [26-93] | 64.4 (15.4) [26-93] | 61.0 (12.0) [29-83] |  |
| Patient Group *(Neglect, Control)* | 73, 149 | 40, 63 | 33, 86 |  |
| Days between Stroke & Imaging | 3.0 (3.2) [0-14] | 2.8 (3.1) [0-14] | 3.1 (3.3) [0-14] |  |
| Aetiology *(Infarct, Haemorrhage, Both)* | 184, 35, 3 | 79, 22, 2 | 105, 13, 1 |  |
| Lesion volume *(cm3)* | 34.4 (43.7) [0.03-312.6] | 34.7 (45.8) [0.03-312.6] | 34.0 (41.8) [0.08-194.7] |  |
| Days between Stroke & Assessment | 3.8 (2.7) [0-14] | 4.0 (2.5) [0-14] | 3.7 (2.9) [0-14] |  |
| Letter CoC | 0.15 (0.26) [-0.06-0.99] | 0.16 (0.27) [-0.02-0.99] | 0.14 (0.26) [-0.06-0.96] |  |
| Bells CoC | 0.14 (0.24) [-0.11-0.92] | 0.14 (0.23) [-0.10-0.92] | 0.15 (0.25) [-0.11-0.91] |  |
| Mean CoC | 0.15 (0.25) [-0.04-0.99] | 0.16 (0.25) [-0.02-0.99] | 0.15 (0.26) [-0.04-0.91] |  |
| Copying Errors | 1.12 (1.88) [0-7] | 1.13 (1.81) [0-7] | 1.11 (1.93) [0-7] |  |
| Visual field defects *(N)* | 36 | 16 | 20 |  |

**Table 1.1:** Clinical and demographic data of the patient sample

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Total  (N = 222) | Neglect (N = 73) | Control  (N = 149) | p-value |
| Age *(years)* | 62.6 (13.8) [26-93] | 65.1 (13.9) [29-93] | 61.3 (13.6) [26-88] |  |
| Sex *(F, M)* | 103, 119 | 40, 33 | 63, 86 |  |
| Days between Stroke & Imaging | 3.0 (3.2) [0-14] | 3.4 (3.5) [0-14] | 2.7 (3.0) [0-14] |  |
| Aetiology *(Infarct, Haemorrhage, Both)* | 184, 35, 3 | 55, 15, 3 | 129, 20, 0 |  |
| Lesion volume *(cm3)* | 34.4 (43.7) [0.03-312.6] | 63.8 (43.7) [0.03-312.6] | 19.9 (23.7) [0.08-138.1] |  |
| Days between Stroke & Assessment | 3.8 (2.7) [0-14] | 4.0 (2.9) [0-14] | 3.8 (2.7) [0-14] |  |
| Letter CoC | 0.15 (0.26) [-0.06-0.99] | 0.42 (0.3) [-0.06-0.99] | 0.02 (0.06) [-0.06-0.78] |  |
| Bells CoC | 0.14 (0.24) [-0.11-0.92] | 0.39 (0.28) [-0.10-0.92] | 0.03 (0.07) [-0.04-0.80] |  |
| Mean CoC | 0.15 (0.25) [-0.04-0.99] | 0.41 (0.29) [-0.04-0.99] | 0.02 (0.07) [-0.04-0.80] |  |
| Copying Errors | 1.12 (1.88) [0-7] | 2.93 (2.31) [0-7] | 0.26 (0.61) [0-4] |  |
| Visual field defects *(N)* | 36 | 17 | 19 |  |

Thus, the study included a total of 222 right-hemispheric stroke patients, comprised of 103 female and 119 male patients (46.87% female, 53.13% male). The mean age at stroke was 62.6 years (SD = 13.8 years) overall, while for women it was 64.4 years (SD = 15.4 years) and 61 years (SD = 12 years) for men. 184 of the 222 patients experienced an infarct/ischaemic stroke (F = 79; M = 105), while 35 patients suffered from a haemorrhagic stroke (F = 22; M = 13) and 3 patients experienced a combination of ischaemic and haemorrhagic strokes (F = 2; M = 1).

A total of 73 were diagnosed with visuospatial neglect, meaning that they exceeded the threshold in at least 2 out of the 3 diagnostic tests (see [2.2. Behavioural Data](#_Behavioural_Data) for details). 40 neglect patients were women, while the remaining 33 were men.

36 of the included patients exhibited primary visual field defects. 28 patients (F = 13; M = 15) were diagnosed with hemianopia, 7 with quadrantanopia (F = 2; M = 5) and one female patient was blind in her left eye.

(see appendix ? for a full list)

### Behavioural Data

The behavioural data were collected by members of our group. Three commonly used diagnostic tests were used for the visuospatial neglect examination: the Letter Cancellation Task ([Weintraub & Mesulam, 1985](#weintraubmesulam1985)), the Bells Cancellation Zest ([Gauthier, Dehaut & Joanette, 1989](#gauthier1989)) and a copying task (source; see [Rorden & Karnath, 2010](#rordenkarnath2010) for an overview). The patients completed those tasks as standard paper-and-pencil tests.

In the cancellation tests, patients are tasked with cancelling all target stimuli that are spatially distributed on a horizontally oriented 21 x 29.8 cm sheet of paper fixated at the centre of the patient’s sagittal midline. In the Letter Cancellation Task, the targets are 60 instances of the letter “A”, which are distributed among other distractor letters, while in the Bells Test the targets are bell icons distributed among other distractor symbols. Patients received no time limit for completing these tasks and were asked to confirm twice that they were content with their performance before ending the tasks.

For our analyses, we calculated the Centre of Cancellation (CoC; [Rorden & Karnath, 2010](#rordenkarnath2010)) values individually for every patient. The CoC is a continuous score ranging from -1 to +1, which describes the number of missed items and their corresponding location. A score of -1 denotes a severe right-sided neglect, while a score of +1 is interpreted as severe left-sided neglect. A The individual CoC values were then compared to a cut-off value (0.083 for the letter cancellation test and 0.081 for the bells cancellation test, respectively). Any value above the cut-off was seen as pathological and interpreted as a potential indicator for visuospatial neglect.

In the copying task, the number of errors made while copying the original figure was counted and a score of at least 2 out of 7 possible errors was deemed pathological. If a patient exhibited pathological behaviour in at least 2 of the 3 tests, they were diagnosed with visuospatial neglect for the purposes of this study (see appendix ? for a full list).

[mean z-value 🡪 calculated on “all” group level to ensure comparability between groups, since they do not differ significantly (t-test)]

Patients were assessed for primary visual field tests (hemi- or quadrantanopia or blindness of one eye) via standard neurological confrontation testing.

### Neuroimaging Data

We used the neuroimaging data acquired during the patients’ clinical investigation at the Centre of Neurology Tübingen. Since those scans were acquired for diagnostic and medical purposes and we did not have any influence on their modality or when the images were acquired. Thus, we included structural imaging of different modalities in this study. Out of the 222 total scans, 105 were CT scans, the remaining 117 were MR scans. On average, scans were acquired 3.0 days (SD = 3.2) after stroke.

If images of multiple modalities were available for a patient, MR scans were preferred. In patients with available MR scans, we preferably used diffusion-weighted imaging (DWI) for scans acquired within the first two days after stroke onset (n = 15) and T2-weighted fluid attenuated inversion recovery (T2FLAIR) images for images acquired at a later point (n = 55). For the remaining patients (n = 45), we used a combination of two modalities (e.g., DWI and T1; see appendix ? for a full list).

The neuroimaging data were pre-processed using MATLAB R2016b and R2020a 64bit ([MathWorks](https://se.mathworks.com/products/matlab.html)) and SPM12 toolbox ([Wellcome Department of Cognitive Neurology, London](https://www.fil.ion.ucl.ac.uk/spm/software/spm12/)). We generally followed the guidelines to lesion-behaviour mapping as described in [de Haan and Karnath, 2018](#dehaankarnath2018) and [Karnath et al., 2019](#karnath2019).

If multiple images of different modalities were available for a given patient, the corresponding images were co-registered using the SPM12 function as a first step. If only a single image was available, this step was skipped.

Then, the Clusterize toolbox ([de Haan et al., 2015](#dehaan2015)) was used to semi-automatically delineate each patient’s lesion. The toolbox’s algorithm first automatically detects potential lesions, i.e., hyper- or hypointense areas, by clustering the image according to a previously selected intensity threshold. The areas flagged by the algorithm as potential lesions are then manually reviewed, selected and modified. This results in a voxel-based binary lesion map. For patients that suffered from both a haemorrhagic stroke as well as an infarct, and as a result exhibited two lesions of different intensities (typically hyperintense for the haemorrhage hypointense for the stroke), the Clusterize algorithm was applied separately for each intensity. Afterwards, the corresponding lesion maps were added and corrected for potential overlaps using a custom MATLAB script. Every patient’s resulting lesion map was visually inspected for its correctness by overlaying it on top of the anatomical scan using the MRIcroN software ([Rorden & Brett, 2000](#rordenbrett2000); [NITRC, 2008](https://www.nitrc.org/projects/mricron/)).

Thereafter, the Clinical toolbox ([Rorden et al., 2012](#rorden2012); [NITRC, 2014](https://www.nitrc.org/projects/clinicaltbx)) was used to normalise every patient’s anatomical scan, as well as the previously created lesion map, to MNI space (Montreal Neurological Institute; SOURCE) with the standard voxel size of 1 mm3. We used this toolbox for the normalisation process rather than the SPM12 normalisation function, since it allowed us to normalise the scan to an age-matched template. We used enantiomorphic correction to control for the lesions during the normalisation process (cf. [Karnath et al., 2019](#karnath2019)). Afterwards, we masked the extracerebral space, as well as the lateral ventricles and cerebellum to optimise the normalisation using a custom MATLAB script. Lastly, the quality of the normalisation was manually checked for every patient’s scan by comparing the normalised brain to the template brain of the given image modality using MRIcron.

### Data Analysis

### Clinical Data/Stroke Aetiology

### Voxel-based Lesion-Behaviour Mapping / Lesion Analysis

We first used MRIcron ([Rorden & Brett, 2000](#rordenbrett2000); [NITRC, 2008](https://www.nitrc.org/projects/mricron/)) to create descriptive overlap and subtraction lesion plots for all relevant groups. Overlap plots are topographies of all patients’ normalised lesion maps. Only voxels that are damaged in at least 5 patients (25% of all voxels) are depicted and used for further analyses.

Subtraction plots are maps that showcase which areas of the brain exhibit lesions more frequently in one patient group (typically with the cognitive deficit of interest) compared to another one (without the deficit of interest).

* Overlay Plot
* Subtraction Plot
* NiiStat: mass univariate voxelwise statistical comparison

### Whole-brain disconnectivity mapping

We used the Lesion Quantification Toolkit (LQT; Griffis et al., 2021) to create individual white matter disconnectivity topographies for every patient. Using the toolkit’s standard HCP-842 tract-wise connectome atlas (Yeh et al., 2018), all fibre streamlines intersecting with a patient’s lesion maps were identified. Subsequently, all connectome-based disconnections that were caused by the lesion were mapped, which allows to topographically assess the impact a lesion has on whole-brain connectivity.

* Mass univariate with NiiStat: No voxels survive (all/female/male)

### Region-to-Region disconnectivity

Once again using the LQT (Griffis et al., 2021), we analysed the lesion-induced disconnectivity on a parcellation-level to identify which direct disconnections between two grey matter regions are significantly associated with increased (i.e., pathological) scores in the behavioural tasks. We chose the Brainnetome atlas (BN-246; Fan et al., 2016) as our parcellation atlas, as it was specifically developed for connectivity analyses and includes cortical (n = 210), as well as subcortical (n = 36) regions. We combined this with the HCP-842 tractography atlas provided by the LQT to generate structural disconnectivity matrices for every patient.

Using custom MATLAB scripts, we analysed associations between parcel-wise disconnections and behavioural scores by employing mass-univariate general linear models (GLM). For this, we firstly loaded the symmetric 246-by-246 disconnectivity matrices into MATLAB and removed the diagonal and elements below it. We also removed any ROI-to-ROI disconnections that are either (physiologically) non-existent in the patient sample or are present in less than 20% of the patient sample (n(all) = 45; n(female) = 20; n(male) = 25) (SOURCE). After removing those data, we computed a GLM for the remaining ROI-to-ROI connections, using the disconnectivity score as the independent variable and the behavioural score as the dependent variable. We calculated 50.000 permutations and computed the maximum statistic permutation (????). This yielded a one-sided corrected threshold at different statistical significance levels.

## Results

### Clinical and Demographic Data

The mean age at stroke was higher for women than for men. This finding was consistent across all groups (i.e., all patients, neglect patients, control group). [calculate significance]

For both the all patients and the neglect patients groups, the mean normalised lesion volume was lower for women than for men. Only in case of the control group did women exhibit marginally larger lesions. [calculate significance]

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Neglect | | Control | | p-value |
| Female | Male | Female | Male |
|  |  |  |  |  |  |

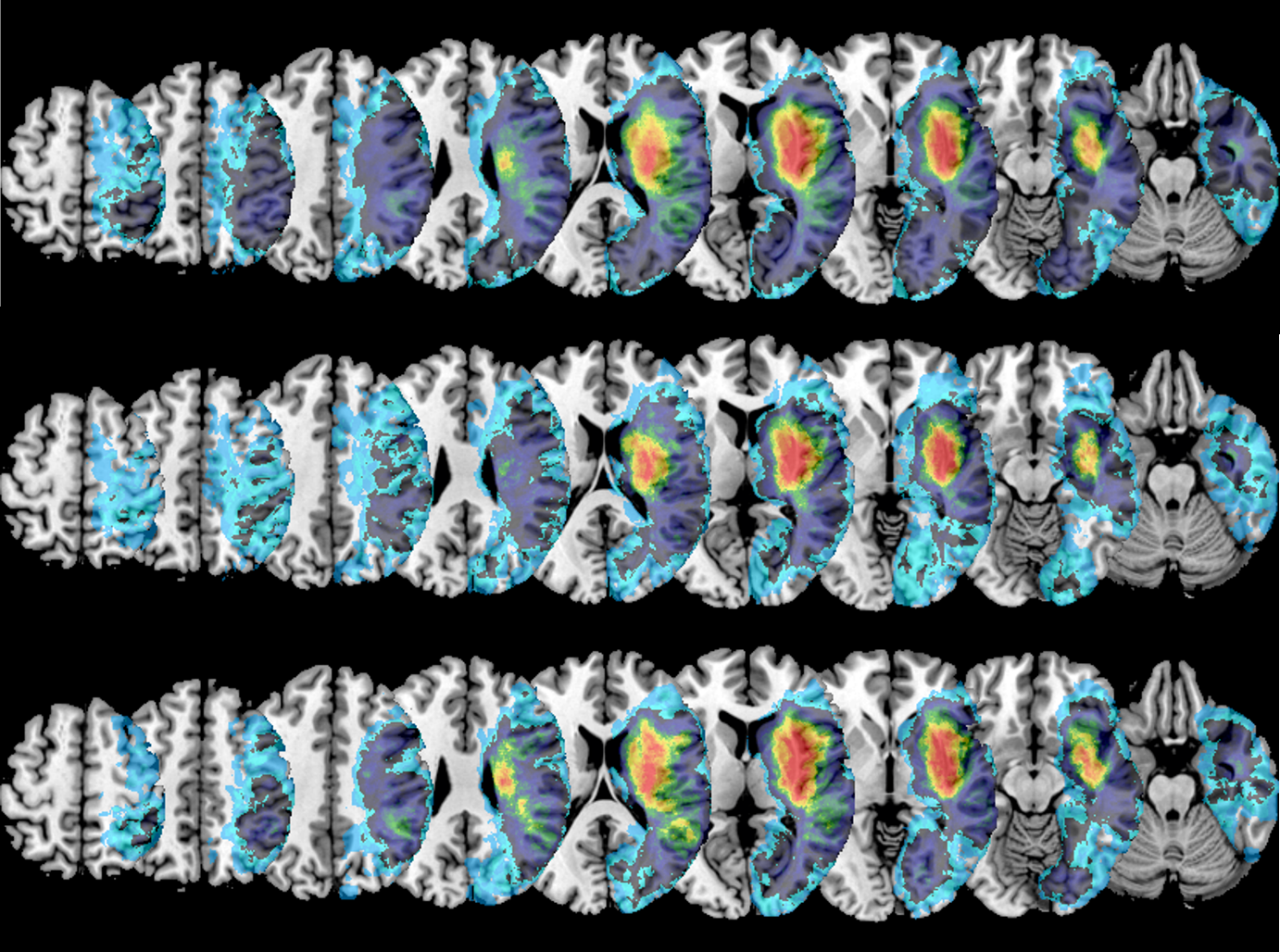
[description]

[create mean age/sex across groups bar graph]

### Voxel-based Lesion-Behaviour Mapping / Lesion Analysis

* Overlay plots

We used MRIcron ([Rorden & Brett, 2000](#rordenbrett2000); [NITRC, 2008](https://www.nitrc.org/projects/mricron/)) to create topographies of the normalised acute lesion overlaps for all relevant groups (see figure 1). Only voxels lesioned in at least 5 patients were included in the subsequent analyses.



* Subtraction Plots
* NiiStat

### Whole-brain disconnectivity mapping

* 1. Region-to-Region disconnectivity

## Discussion

## Conclusion

## References

[delete this later]

**MRIcron** -> Rorden & Brett, 2000

**Clusterize** -> de Haan et al., 2015

**Clinical** -> Rorden et al., 2012

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## Appendix

### Appendix A: List of Abbreviations

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| CoC | Centre of Cancellation |