Unravelling the high-dimensional structure of spatial neglect and visuospatial attention: A multivariate approach to lesion-behaviour mapping

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花より団子

Hana yori Dango

Abstract

One of the most studied and elaborated neurological disorders after stroke is probably spatial neglect, a disorder of spatial exploration, attention and awareness occurring in about two third of all right hemispheric stroke patients. A characteristic symptom these patients show is a failure to orient or respond to information on the contralesional side of space including a general orientation to the ipsilesional side. It is still not possible to come to a common consensus regarding this syndrome on theoretical, anatomical and behavioural aspects. The investigation of the anatomical substrates of spatial neglect, however, offers chances to shed light on crucial pathophysiological processes and inform theoretical models. Therefore, a complete research field dedicated several decades of research to the question where in the brain the syndrome of spatial neglect might have its´ pathogenesis and how this information can help us to understand cognitive processes of normal spatial exploration and attentional processing. A method which largely contributed to this field is called lesion-behaviour mapping by drawing statistical inference about the functional brain architecture from focal brain damage. Following the development within the last five to ten years, a new era of computerised lesion-behaviour mapping techniques became widely available, allowing to reiterate and challenge previous findings and to account for the high-dimensional information present in brain lesions. In my thesis I employed these new techniques to unravel the anatomical substrates of the syndrome of spatial neglect and related spatial attentional deficits. I want to show that these methods can be deployed to make valuable contributions to the understanding of the pathophysiology of the syndrome. In my first empirical work, the presence of a large right-hemispheric network related to the behavioural severity of spatial neglect can be confirmed, closing longstanding controversies. It shows that multivariate machine-learning based lesion-behaviour mapping techniques are particularly suited to detect critical brain areas and to evaluate the predictive performance of underlying statistical models. In the second and third empirical work, I complemented these primary findings by applying the same statistical methodology to parameters of remote disconnection and to different diagnostic tools in the assessment of spatial neglect. These works show crucial areas and anatomical hubs severely disconnected to other areas of the brain and contributing to the development of lateralised deficits in spatial neglect patients. Finally, with the last empirical work, contributions to controversial views concerning the anatomical substrates of the

extinction phenomenon, a further spatial attentional deficit, were made. By evaluating lesion-behaviour relationships in spatial neglect, as it was done in the present thesis, it will become possible to inform clinical staff how to direct patients to more effective management and treatment schedules, essential for rehabilitation, while spatial neglect generally is considered as a negative prognosis factor for stroke recovery.

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Abbreviations

ALE	Activation Likelihood Estimation
BIT	Behavioral Inattention Test
CBS	Catherine Bergego Scale
CT	Computed tomography
cTBS	Continuous transcranial inhibitory brain stimulation
CoC	Center of Cancellation
DTI	Diffusion Tensor Imaging
dTLVC	Direct Total Lesion Volume Control
FDR	False Discovery Rate
FWE	Family-Wise Error
fMRI	Functional magnetic resonance imaging
LBE	Line Bisection Error
MCA	Middle Cerebral Artery
MRI	Magnetic Resonance Imaging
MLBM	Multivariate Lesion Behaviour Mapping
PCA	Principal Component Analysis
SVM	Support Vector Machines
SVR	Support Vector Regression
SVR-LSM	Support Vector Regression Based Lesion-Symptom Mapping
SVR-DSM	Support Vector Regression Based Disconnection-Symptom Mapping
SVR-CLSM	Support Vector Regression Connectome Lesion-Symptom Mapping
SWM	Spatial Working Memory
VBM	Voxel-Based Morphometry
VLBM	Voxel-Based Lesion Behaviour Mapping

1 General Introduction

"Oh, I think you forgot to put on your left slipper! "

That is what I said to a patient which I guided to an examination room after recognising that he walked barefoot through the corridor. At that time, I was an intern in a neurological rehabilitation centre and I was just having my first contact with a patient suffering from spatial neglect. This patient presented further symptoms in daily routines, for example, the left side of his body collided regularly with the door frames of the hospital, he spared some of the food on the left side of the plate and orientated his head by default to the right side in reference to his body centre. Surprisingly this patient was not aware of his condition although it clearly affected his life. The patient was left-handed and worked as a passionate cook, but to my knowledge never was able to return to his job.

This case is a prominent example of a subgroup of stroke patients with predominantly right sided brain damage. Already at this early stage of my neuropsychological and neuroscientific career, I was fascinated by the clinical presentation of that patient. Traditionally, such clinical observations are the heart of neuropsychological research and the first starting point of intensive research. I was particularly interested in how selectively and to what extent the brain needs to be damaged to produce such a circumscribed deficit in spatial cognition.

Hence, after an intense literature research I recognised that I was not yet able to understand the pathophysiological mechanisms of the condition and I was particularly overwhelmed by the number of publications, the various theories and to some extent also the contradictory findings. It seemed that most researchers implicitly agreed that spatial neglect is caused by damage to several areas of the right hemisphere notably of the territory of the middle cerebral artery blood supply. A real consensus, however, on concrete brain areas could not be established. It was quite frustrating to discover that after more than several decades of neuropsychological research, there was still this lack of clarity. Nonetheless, I also realised that the aim to achieve this seems to be very ambitious. It turned out that the syndrome of spatial neglect is extremely complex, and characteristic symptoms which easily attract most clinicians´ attention – analogous to that what I experienced with the aforementioned patient – can be considered as the tip of the iceberg.

Finally, when I started my further career, I decided to dedicate my doctoral thesis to this research field. As a greater goal, my thesis deals with the study of stroke patients, the syndrome of spatial neglect and notably the question what stroke anatomy can tell us about the disorder, related deficits, normal spatial exploration and attention. To this aim I devoted a considerable amount of time to the comprehension and application of advanced neuroimaging techniques like lesion-behaviour mapping.

In the synopsis of my thesis, I first give a general introduction into the research field of spatial neglect (chapter 2) and I discuss cardinal symptoms and diagnostics. In chapter 3, I provide an overview of current theoretical models of spatial neglect. In chapter 4, I discuss some historical landmarks in spatial neglect research, the precursors of lesion-behaviour mapping and I give an introduction to this method. Moreover, in this chapter, I describe the transition from traditional to a new era of advanced analysis techniques and I provide a rationale for the application of these new techniques to the syndrome of spatial neglect. In chapter 5, I give a short overview on the empirical investigations in my thesis. Finally, in chapter 6, I present future research directions in the field and discuss clinical implementations.

2 Introduction to spatial neglect

2.1 Egocentric Core Symptoms

Spatial neglect is one of the most common syndromes after unilateral brain injury of predominantly the right hemisphere (Becker and Karnath, 2007; Stone et al., 1993; Ten Brink et al., 2017), especially after stroke and is mainly considered to be a disorder of spatial attention (Corbetta et al., 2008, 2005). In general patients fail to attend or to react to information on the contralesional side of the space (Heilman et al., 1983; Karnath and Rorden, 2012). In the acute stage of a stroke, patients often do not react when they are approached from the contralesional side and a large portion of neglect patients show a deviation of their head and eye-in head position at rest to the ipsilesional side (Becker and Karnath, 2010; Fruhmann-Berger et al., 2006; Fruhmann-Berger and Karnath, 2005), even in pure darkness (Karnath and Fetter, 1995). It is important to note that these deficits can only be explained by the syndrome if they cannot be attributed to primary motor or sensory failure (Heilman and Valenstein, 1979). In general, spatial neglect is a negative prognosis factor for stroke recovery (Denes et al.,

1982; Jehkonen et al., 2007, 2000) and as patients often exhibit no insight into this deficit (i.e. anosognosia), the negative impact on daily life is further exacerbated (Appelros et al., 2003, 2002; Cumming et al., 2009). As explained above, the core symptoms are represented typically on the visual modality and with reference to the own egocentre, which means with reference to the own body position and trunk axis. Thus, although several authors consider spatial neglect as a syndrome consisting of various component deficits (Driver et al., 2004; Vuilleumier, 2013; Vuilleumier et al., 2007), egocentric neglect and hence, the spontaneous and sustained deviation of eyes and head towards the ipsilesional side, combined with omission of contralesionally located information or targets, can be defined as the egocentric core components of the disorder (Corbetta and Shulman, 2011; Karnath and Rorden, 2012).

2.2 Nosological overview of lateralised symptoms in spatial neglect

In general, symptoms associated to spatial neglect can be distinguished along different modalities (i.e. sensory, motor, auditive, representational), along various reference frames (i.e. allocentric, egocentric) and/or along directionality of information (i.e. afferent/efferent). For example, patients do not only show deviations in the visual modality, but also during tactile, auditory or motor tasks. Patients might ignore or mislocalise tactile, thermal or painful stimulations (Liu et al., 2011), when they are applied to the contralesional body side and they ignore or mislocalise sounds coming from the left side of the space (Pavani et al., 2004). Correspondingly proprioception can be affected in spatial neglect patients, which was shown by Vallar et al. (1995). The authors asked subjects with spatial neglect to evaluate the orientation of their upper limbs after moving them into different positions. This manipulation showed a perceptual deficit of position sense for the contralesional limb in these patients. A small subset of spatial neglect patients also show difficulties in the execution of movements to the contralesional side or a general reduction in the spontaneous use of contralesional limbs (i.e. motor neglect), even when the motor system of the patient is spared (Sampanis and Riddoch, 2013). Nevertheless, these patients are generally able to move their contralesional limbs, especially when they are encouraged (Garbarini et al., 2013). Although this is quite rare, motor neglect can occur also during the absence of visuospatial core symptoms of the syndrome (Punt et al., 2005).

According to the distinction in reference frames, behavioural deficits in spatial neglect can be divided into 2 major groups: allocentric (stimulus- or object-centred)

neglect and egocentric (eye-, head- and trunk-centred) neglect. Patients with allocentric neglect omit or ignore, for example, the left part of an object in uni-, bi- or tridimensional space, irrespective of the location of these objects in relation to the patients´ viewpoint. Whereas several authors argued that egocentric and allocentric neglect can dissociate (Hillis, 2005), newer studies are reporting considerable associations and/or interactions (Li et al., 2014; Rorden et al., 2012b; Yue et al., 2012). The egocentric position can, for example, modulate allocentric perception and can result in a more severe allocentric bias if stimuli are presented in the contralesional space (Li et al., 2014).

Finally, symptoms in all these modalities might not only be present in the real external world, but also in the sole imagery and mental representations of the patient, which is termed as representational neglect. Hence, when patients are asked to recall a familiar scene from memory, content from the contralesional side is not or only incompletely reported (Bisiach and Luzzatti, 1978).

2.3 Further spatial and non-spatial deficits and disorders related to spatial neglect

2.3.1 Extinction

Extinction is a frequently occurring disorder of spatial attention and typically a consequence of right hemisphere injury (Becker and Karnath, 2007). Patients with visual extinction are able to report single unilateral visual targets in either visual field but are unable to report a contralesional target in bilateral (i.e. multi-target) conditions where an ipsilesional target is concurrently present (de Haan et al., 2012; Oppenheim, 1885). Extinction was often defined as a residual form of spatial neglect and indeed, results from a longitudinal case study by Bonato et al. (2015; 2012) seem to confirm this assumption. The authors showed that a patient with spatial neglect who performs normal on traditional paper and pencil neglect assessments can still present an extinction phenomenon with increasing task demands 3 years after stroke onset. However, what the authors consider as visual dual task to detect residual spatial neglect, is in fact an extinction task with simultaneous bilateral target presentation. It is important to be aware of the fact, that behavioural differences exist between the extinction phenomenon and spatial neglect. Accordingly, a considerable amount of neglect patients do not show any signs of extinction at all in the acute or chronic phase

of the stroke and even double dissociations on behavioural tasks were reported (Hillis et al., 2006; Posner et al., 1984; Rees et al., 2000; Vossel et al., 2011; Vuilleumier and Rafal, 2000). From an anatomical view, a dissociation in behaviour cannot be clearly localised in the brain, as extinction is linked to lesions in the parietal, occipital, and temporal lobules, areas which are also reported to underlie spatial neglect (Chechlacz et al., 2013; Hillis, 2005; Karnath et al., 2001; Karnath and Rorden, 2012; Rengachary et al., 2011; Vossel et al., 2011). Altogether it seems, however, – in contrast to anatomical findings in spatial neglect – that the anatomical correlates of extinction mainly centre around the temporo-parietal junction. Still, there is a large heterogeneity in the reported studies and final conclusions cannot be drawn. In the present thesis in project 4: '*Anatomical substrates of visual extinction: A multivariate lesion analysis study in acute stroke*', I aim to contribute to (i) the demarcation of areas responsible for visual extinction and (ii) the differentiation of spatial neglect from extinction from a neuroscientific perspective.

2.3.2 Spatial Working Memory

Spatial working memory (SWM) impairment is discussed as playing an important role in spatial neglect (Striemer et al., 2013). Working memory is typically defined as the ability to hold information online after it was removed from view, and it is thought to have a limited capacity (for review, see Baddeley, 2012). With reference to a spatial sub-component, SWM can be seen as the ability to maintain spatial information over short time frames (Striemer et al., 2013). Clinically, spatial neglect patients cross out targets in cancellation tasks multiple times and return more frequently to ipsilesional areas of the working sheet. A deterioration of SWM performance in neglect patients can be demonstrated in both spatially lateralised and non-lateralised tasks (Ferber and Danckert, 2006; Malhotra, 2004; Mannan et al., 2005; Mort et al., 2003; Pisella et al., 2004). However, the question whether deficits in SWM are part of the core symptoms of spatial neglect cannot easily be answered. Evidence from neuroimaging studies show that processes of working memory and (spatial) attention are both localised in fronto-parietal networks (Awh and Jonides, 2001; Malhotra et al., 2009). Thus, it is possible that SWM deficits only co-occur frequently in this patient group and there might be no particular interactions with the typically lateralised core symptoms in spatial neglect.

2.3.3 Additional non-lateralised deficits

Further non-neglect specific impairments often coexist with the neglect syndrome but can be considered as general consequences after left or right brain damage (Husain and Rorden, 2003) and hence, are not neglect specific. Thus, spatial neglect patients typically show impairments of arousal (Robertson et al., 1997), in visual processing capacity (Husain et al., 1997) of sustained attention (Rueckert and Grafman, 1996), of selective attention (Raymond et al., 1992), an impairment in keeping track of spatial locations across saccades (Duhamel et al., 1992; Heide et al., 1995) and a general bias towards local visual features (Lamb and Robertson, 1988). Furthermore, many neglect patients are not aware of their deficits (i.e. anosognosia) (Bisiach et al., 1986; Cutting, 1978; Orfei et al., 2009; Pedersen et al., 1997; Stone et al., 1993; Vallar et al., 2003).

2.4 Diagnostic procedures to detect lateralised spatial biases after stroke

Following the scientific literature, spatial neglect can in general be tested by a variety of diagnostic tools or neuropsychological test batteries. The application of large test batteries might, however, not be feasible, especially in acute stroke patients who are not able to follow complex instructions or show limited cognitive resources. Therefore, in most clinical routines, brief and convenient bedside tests were implemented. It was shown that these screening tasks are sensitive enough to detect symptoms typically related to spatial neglect (Azouvi, 2002; Ferber and Karnath, 2001a; Halligan et al., 1989). Nevertheless, there is no consensus on the concrete tasks to be used and in different institutions or clinical wards, spatial neglect is assessed by a variety of tests. In most cases, clinicians decide on the diagnosis only after using multiple tasks to account for different clinical manifestations and/or they subsume the outcomes of multiple tasks into one component score. This approach ignores that some procedures are unable to capture the spatial egocentric core deficits. Furthermore, it is possible that a patient shows a pathological score in one test, whereas the same patient appears completely normal in others (Buxbaum et al., 2004). Some of the diagnostic procedures are closely related, whereas others are loading together on several rather unrelated factors, which was demonstrated by performing factorial analysis (Saj et al., 2012; Vaessen et al., 2016; Verdon et al., 2010). Correlations between test scores vary considerably from low to relatively high correlations (Ferber and Karnath, 2001a; Guariglia et al., 2014; Halligan et al., 1989; Molenberghs and Sale, 2011; Sperber and

Karnath, 2016a). Even a very simple diagnostic procedure, as for example the line bisection test (see section 2.4.1, *'Line Bisection'*) can load on two very different factors, as recently demonstrated by McIntosh et al. (2017, 2005). Specifically, the authors argued that the outcome in the traditional line bisection assessment is influenced by a factor correlating with spatial egocentric core symptoms of spatial neglect (as defined by Corbetta and Shulman, 2011; Karnath and Rorden, 2012; and in the present thesis), but also by a second factor representing general attentional capabilities (McIntosh et al., 2017). Without being aware of these two factors, the test outcome may be interpreted as lateralised bias in spatial neglect, although patients present only general attentional deficits. This reflects different conceptions and theories about the syndrome. Whereas some authors argue that the leading mechanism in spatial neglect is a bias in spatial attention related to an interhemispheric functional imbalance, other authors argue that neglect might be a representational error or caused by an erroneous integration and transformation of spatial coordinates from multisensory input (see chapter *'3 Models of Spatial Neglect'*). Similarly, there are authors preferring one test over the other to capture symptoms, reflecting their conception of the disorder. This, however, might contribute to the assumption that spatial neglect is a heterogenous phenomenon and hence, was denoted as "meaningless entity" (Halligan and Marshall, 1992). The efforts of some research groups to unify all these attentional, non-attentional, lateralised and non-lateralised symptoms after right hemispheric stroke together under the same term "spatial neglect" had a large impact on the conclusions drawn from these outcome variables after clinical testing. Bowen et al. (1999) reported, for example, that the frequency of occurrence of neglect in patients with right brain damage may vary with respect to the assessment. For lesion-behaviour mapping, this means that choices on clinical tests and criteria for evaluation of these tests can have an impact in the detection of the anatomical correlates of a behavioural syndrome (Saj et al., 2012; Toba et al., 2018; Vaessen et al., 2016; Verdon et al., 2010; Vuilleumier, 2013) and hence, might have contributed to contradictory anatomical findings in the literature of spatial neglect (for discussion, see Sperber and Karnath, 2018). As noted by Saj et al. (2012), pooling the results of various diagnostic procedures into one compound score to perform lesion-behaviour mapping might blur the signal and increase noise in the dependent variable, reducing the statistical power for some areas to be detected. This can increase the risk to delineate areas related to an unspecific factor, for example, vasculature or lesion volume. Therefore, I strongly argue for using

behavioural scores of single tests rather than complex component entities in order to conduct anatomo-behavioural investigations. If single tests are well conceived and reflect a good internal validity, interpretation of topographical findings is eased and results can be linked precisely to the clinical behaviour.

By using multivariate lesion-behaviour mapping to map the anatomical correlates of two commonly used diagnostic procedures in isolation, I aim to resolve current discrepancies existing in the literature between these tasks. In the next section I present three behavioural tasks in detail which are used in the present thesis. Moreover, I provide a short overview on other clinically relevant test procedures. The first test is the line bisection test (Schenkenberg et al., 1980), which is still regularly used in the diagnosis of spatial neglect, although its diagnostic validity was challenged (Sperber and Karnath, 2016a). Second, I introduce cancellation tasks, more specifically the Letter Cancellation Task (Weintraub and Mesulam, 1985) and the Bells Cancellation Task (Gauthier et al., 1989). Combined with the derivation of the Center of Cancellation score (CoC; Rorden and Karnath, 2010), these tasks can reliably capture the egocentric core component of spatial neglect (Corbetta and Shulman, 2011; Karnath and Rorden, 2012). Finally, I introduce a common approach to assess extinction. Although extinction and spatial neglect dissociate in behaviour (Becker and Karnath, 2007; Vossel et al., 2011), they often occur with similar incidence and can be present simultaneously.

2.4.1 Line Bisection

The line bisection task is one of the oldest approaches traditionally used to diagnose visual field defects. Axenfeld (1894) used the task to evaluate homonymous hemianopia by detecting a spatial bias in bisecting horizontally arranged lines on a sheet of paper. The task was adopted several years later to investigate spatial neglect (Heilman and Valenstein, 1979; Schenkenberg et al., 1980) and is now part of most neuropsychological test batteries (e.g., Halligan et al., 1991; Vaes et al., 2015) as it is easy to administer as a bedside protocol even in the hyperacute stage of a stroke. In its currently most used form, patients are asked to strike the centre of horizontal lines shown to the patient. An ipsilesional deviation from the true centre of the line is considered to be a sign of spatial neglect and defined as line bisection error (LBE). However, the performance in line bisection not always correlates with the visual core symptoms of spatial neglect as explained in the introductory paragraph of this chapter

and dissociations were reported (Halligan and Marshall, 1992; Marshall and Halligan, 1995).

In Sperber and Karnath (2016a), after conducting an empirical evaluation of the validity of the line bisection task in a large dataset of 180 acute right hemispheric stroke patients, the authors stated that "*… the line bisection task does not appear to be a valid task to diagnose neither primary visual field defects nor spatial neglect …"*. Indeed, in right brain damaged patients with hemianopia and spatial neglect one would expect that both deficits should cancel each other out, as the effects should be diametrical to each other. However, in patients with both disorders the ipsilesional LBE can be more pronounced compared to patients suffering from spatial neglect only (Daini et al., 2002; Doricchi et al., 2002; Doricchi and Angelelli, 1999; Sperber and Karnath, 2016a).

Following all these findings, the line bisection task seems to produce puzzling results and one may ask if the typical LBE arises from other factors than those responsible for spatial neglect. Indeed, as explained above, McIntosh et al. (2017, 2005) suggested a two-component theory for the line bisection task and argued that the traditional line bisection assessment might provide only a biased and noisy evaluation of the spatial bias in neglect patients. On a behavioural level, the LBE may dissociate from typical neglect measures (Azouvi, 2002; Binder et al., 1992; Ferber and Karnath, 2001b; McGlinchey-Berroth et al., 1996; McIntosh et al., 2017; Sperber and Karnath, 2016a; Toba et al., 2017; Verdon et al., 2010). Such dissociations are further detectable on an anatomical level (Binder et al., 1992; Rorden et al., 2006; Thiebaut De Schotten et al., 2014; Vaessen et al., 2016; Verdon et al., 2010), although topographical findings between these investigations vary considerably.

As anatomical findings of the LBE are still contradictory, I reiterate this topic in project 3 of the present thesis: '*Disconnection somewhere down the line: Multivariate lesion-symptom mapping of the line bisection error*'. Moreover, I discuss in this work if the anatomical network responsible for the core symptoms of spatial neglect, measured through cancellation tasks, differs from the one observed for the traditional line bisection task.

2.4.2 Cancellation tasks

'Cancellation tasks' are another category of diagnostics used to assess spatial neglect. This type of tests was widely distributed by Albert (1973). Cancellation tasks typically are conceived as sheets of paper having spatially arranged targets with or without

distractor items which are presented to a patient with respect to his mid-sagittal body axis. The instructions are simple. Patients are asked to visually scan the whole sheet of paper for specific target items and to cancel them out. For several tests, patients are further asked to detect targets among distractor items. Traditionally, targets on the contralesional and ipsilesional side are counted and contrasted to each other as a marker for spatial biases. Interestingly, researchers do not completely agree on the exact way of evaluating the performance on these tests. Hence, different procedures were suggested ranging from simply counting target hits or omissions like in the behavioural inattention test battery (BIT, Halligan et al., 1991) to procedures deriving lateralization indices as a ratio of ipsilesional and contralesional detected or omitted targets (Friedman, 1992; van Kessel et al., 2010). Further complex mathematical calculations like power functions (Chatterjee et al., 1992) or logistic regression (Chatterjee et al., 1999) were used in order to derive a suitable parameter. However, all these procedures were either not very accurate in detecting the spatial bias in neglect patients or they did not provide a single intuitive measure that can be used as an index of neglect severity. Therefore, Rorden and Karnath (2010) introduced the Center of Cancellation (CoC) score which evaluates the average horizontal coordinate of all cancelled targets minus the average horizontal coordinate of all targets. The CoC score can be derived from every cancellation task and can be considered as a continuous and robust measure of neglect severity.

In the 'Albert´s test' (1973), 40 small target lines are arranged in various orientations and grouped in 7 rows on a sheet of paper (nowadays typically A4 landscape horizontally presented, 21 x 29.7 cm; same for all other cancellation tests). The sheet of paper is presented in front of the mid-sagittal body axis of the patient who is asked to cancel out every line he can see. This test is convenient, as the instructions are very simple and therefore it can be used with severely impaired patients or patients with language disorders. However, due to its simplicity, the test is also prone to ceiling effects. Therefore, further variants were developed, as, for example, the Letter Cancellation Task (Weintraub and Mesulam, 1985) where 60 target letters 'A' have to be detected among other distributed distractor letters and the Bells Cancellation Test (Gauthier et al., 1989) where 35 bell icons distributed all over the sheet between other symbols have to be detected. The Letter and Bells cancellation tasks were used in the appended studies. Note that these tasks mainly capture egocentric biases. For diagnosis of allocentric neglect, Ota et al. (2001) developed the defect detection task, where

patients are asked to first find 20 complete target circles among distractor items and then on a second copy of the test to find 20 incomplete circles. In a similar way as for egocentric neglect and the CoC, Rorden et al. (2012b) developed a simple and efficient routine to derive an allocentric score.

2.4.3 Extinction testing

Especially for bed side testing, an easy procedure was developed for the diagnosis of extinction (Ticini et al., 2010). During the assessment, the patient is required to detect a movement of the examiner's left and/or right index finger presented in the patient's left or right visual field. Following the procedure in the appended projects and also in previous studies (Becker and Karnath, 2007; Karnath et al., 2003; Ticini et al., 2010), in total 10 unilateral left, 10 unilateral right and 10 bilateral movements are presented. The patient needs to tell where movements are detected. The severity of visual extinction can then be determined by calculating the percentage of bilateral trials in which the patient failed to detect a contralesional movement. A reliable parameter can, however, only be derived if the patient is able to perform well for unilateral targets. For this type of task, computerised versions were developed which can be modified to increase working load, but that main procedure in general does not differ between manual or computerised forms. It is important that data about a putative visual field defect is collected a priori, as this requires an adaptation of the task. This can be done by using the common confrontation technique. The confrontation technique is a simple task to diagnose visual field defects, especially hemianopia or quadrantanopia, and it is routinely used in acute stroke populations. The examiner presents a finger at various positions and asks the patient to signal if a movement of the finger is detected. If available, visual field defects can also be detected by computerised perimetry testing, although in clinical routine this is often not possible. In case of patients with lower or upper visual field quadrantanopia, movements for extinction testing need to be presented in the intact upper or lower visual field respectively. In patients with left visual field hemianopia, movements are presented in the near and/or far periphery of the intact visual field.

2.4.4 Further diagnostic procedures

Further diagnostic tasks include, for example, single object copying of simple line drawings (i.e. daisy, clock, star, cross, cube) or multi-object copying of more complex

drawings. Whereas single object copying tasks were not very sensitive (Bailey et al., 2000), multiple object copying tasks (i.e. complex scenes) are much better suited to detect spatial neglect, as shown for the scene copy task by Johannsen and Karnath (2004). Another category of diagnostic procedures exploit the syndrome's impact on activities of daily living, as, for example, for the Catherine Bergego Scale (CBS; Azouvi et al., 2003). Indeed, spatial neglect is a negative predictor of general functional outcome (Nijboer et al., 2014, 2013). However, multitasking or visual scanning are in general not explicitly tested and patients might already use compensatory strategies to overcome lateralised attentional deficits. Moreover, items in these rating scales encompass behaviour on different dimensions, and thus, use a compound score with similar problems as for the aggregation of multiple test scores explained above, which is not suited to perform lesion-behaviour mapping.

Along with the development of computerised tests, new possibilities in terms of diagnostic procedures or derivation of more advanced outcome parameters will become available (e.g. touchscreen-based testing, multi-sensory approaches). However, as these diagnostic procedures are still in development and evidence on sensitivity and specificity is still lacking, more data and studies are needed to be able to establish these new routines in clinical wards and test their value in studies using lesion-behaviour mapping.

2.5 Recovery, Rehabilitation and Therapy

In most stroke patients, spatial neglect recovers within three to twelve months. However, in approximately one third of the patients symptoms of spatial neglect persist beyond that timeline (Campbell and Oxbury, 1976; Cassidy et al., 1998; Colombo et al., 1982; Samuelsson et al., 1997) and can stay even after one year (Nijboer et al., 2013). Interestingly, several factors which might influence the recovery process after stroke were suggested. They include clinical variables, for example, initial severity of neglect, visual field defects and premorbid atrophy but also demographic variables, for example, age (Campbell and Oxbury, 1976; Cassidy et al., 1999, 1998; Colombo et al., 1982; Hier et al., 1983; Jehkonen et al., 2007, 2000; Levine et al., 1986; Stone et al., 1992). A further factor which recently gets more and more into focus in recovery and rehabilitation is the exact lesion pattern (i.e. location, size and remote effects) (Karnath et al., 2011b; Lunven et al., 2015; Lunven and Bartolomeo, 2017; Nyffeler et al., 2019). So far, evidence on specific interventions for treatment in spatial neglect patients is

somewhat sparse and several reviews on that topic failed to formulate clear recommendations on which rehabilitation strategy should be preferred (Azouvi et al., 2017; Liu et al., 2019). Nevertheless, in the German guidelines on rehabilitation of spatial neglect (Karnath, Zhil et al., 2017), which were based on a comprehensive literature research, three strategies were outlined alone or in combination with other techniques and are considered being the most promising procedures so far, (i) active exploration and orientation training to the contralateral side (Antonucci et al., 1995; Kerkhoff, 1998; Pizzamiglio et al., 1998), (ii) neck muscle vibration therapy (Johannsen et al., 2003; Saevarsson et al., 2010; Schindler, 2002) and (iii) optokinetic stimulation (for review, see Hill et al., 2015).

Despite these evidences, several research groups adopt more extreme positions and suggest that recovery of stroke in general might follow a fixed pattern and therapeutic strategies do not add much to the recovery process (Marchi et al., 2017; Ramsey et al., 2017; Stinear et al., 2017; Winters et al., 2017). However, there are a few studies showing clear benefits of single or combined interventions even above this natural recovery process (Nyffeler et al., 2019). Accordingly, there is first evidence that not each intervention is suited for every patient, which might lead in general to large interindividual variability in these studies and false negative findings on a group level. If this is true, we need to focus on individualised therapy and to find predictive markers informing us about the putative effects of specific interventions. This requires adapting study designs by modelling potential markers in addition to main rehabilitation effects, in order to evaluate successful treatments. Accordingly, it was shown that therapy by prism adaption in neglect patients is only effective in patients with thicker cortex in temporo-parietal, prefrontal and cingulate areas of the left, undamaged hemisphere or in individuals with higher structural connectivity in the body and genu of the corpus callosum (Lunven et al., 2019). Similarly, for the treatment by inhibitory continuous theta burst stimulation (cTBS; which is a transcranial magnetic stimulation protocol) over left parietal brain areas, interhemispheric integrity of the corpus callosum needs to be spared by brain damage to be effective in spatial neglect (Nyffeler et al., 2019). These studies show clearly that a comprehensive knowledge about anatomical markers related to the development of a neurological syndrome may help to evaluate and predict long-term recovery and/or direct clinical decisions.

3 Models of spatial neglect

During the last decades, several models to explain the disorder of spatial neglect were suggested. Nevertheless, until today, there is no complete consensus on this. However, as some of these theoretical frameworks are referring to cognitive modules and anatomical structures, a closer look at neuroimaging results might help to evaluate the proposed theories.

3.1 Attentional Models

One of the first models referring to dysfunctional attentional processes in spatial neglect was termed 'imbalance model' or 'orientation bias model' of spatial neglect and was introduced by Kinsbourne (1993, 1970). According to the author, a (predominantly) right inhibitory brain module after right brain damage is not working accurately leading to an over excitation of left inhibitory brain activity, 'pushing' the patients' attention to the ipsilesional side. Moreover, it was suggested that lateralised brain damage produces an ipsilesional oriented vector of attentional capabilities with peaks on the extreme outer positions of attentional gradients. In cancellation tasks, this would be reflected by an increasing number of missed targets from ipsilesional to contralesional and vice-versa for caught targets. Following this idea, Kinsbourne (1993) even assumed that spatial neglect patients should start to turn continuously around their own vertical body axis.

In a similar way, Heilman and van den Abell (1980) suggested that spatial attention is characterised by a right hemispheric dominance. The authors explained that the right hemisphere should be able to direct attentional resources to the right and to the left side of the space, whereas the left hemisphere is only capable to direct attentional resources to the right side of the space. Although this assumption might be far too simple in light of the currently available literature, it could at least explain differences in incidence rates for left and right neglect (Suchan et al., 2012). Accordingly, right neglect with left hemispheric brain damage is rather rare.

From a neuroscientific perspective, supporting evidence for this model came from Corbetta et al. (2005). The authors demonstrated that in neglect patients contralesional intact parietal areas show an increased BOLD (Blood-Oxygenation-Level Dependent) response. While patients recover over time, this BOLD-imbalance between both hemispheres vanishes (Corbetta and Shulman, 2011; He et al., 2007).

According to the latter observation, the inhibition of the overexcitability of left parietal brain areas can be supported by non-invasive brain stimulation (Salazar et al., 2018). Hence, as suggested by Koch et al. (2011) inhibition of the left parietal cortex by cTBS might enable the right hemisphere to normalise its´ activity. Following this and in line with the imbalance model of spatial neglect, disconnection between both hemispheres should then be beneficial for the undisturbed functioning of areas of the right hemisphere engaged in spatial attention. However, the opposite is true (Bartolomeo et al., 2007) and callosal integrity is predictive for behavioural recovery and rehabilitation (Lunven et al., 2019, 2015; Nyffeler et al., 2019). Moreover, although inhibitory contralesional brain stimulation might work on a group level, there is a large interindividual variability and not every patient improves with this approach. In contrast to the suggestion by Koch et al. (2011), not only inhibition but also the up-regulation of left parietal attentional areas was associated to better recovery (Umarova, 2016), suggesting that left parietal brain activity should be facilitated rather than inhibited.

Moreover, despite these findings, Umarova (2011) demonstrated in an fMRI-based investigation that left hemispheric hyperactivation and right hemispheric deactivation, as shown by Corbetta and colleagues (2005), is not neglect specific, but is a general consequence after right hemispheric stroke. Surprisingly, the interhemispheric imbalance might even not be related to spatial attention at all but can reflect a general reorganisational process without any link to specific behaviours (de Haan et al., 2013). The authors found a similar imbalance in stroke patients without neglect engaged in a non-spatial attention task. Furthermore, the abnormal fMRI BOLD response was not related to behavioural performance of the patients. Altogether, findings from different studies do not converge regarding processes of functional interhemispheric imbalances in spatial neglect.

The anatomical findings of the appended projects can further underline a theoretical argumentation against some aspects of the interhemispheric imbalance model in spatial neglect. Although results show that damage to interhemispheric callosal structures in lesion mapping might be linked to the severity of the neglect syndrome (see appended project one: '*Using machine learning-based lesion behavior mapping to identify anatomical networks of cognitive dysfunction: Spatial neglect and attention*'), connectome lesion-symptom mapping (see appended project two: '*Structural (Dis)Connectomics of spatial exploration and attention: a study of stroke*

patients with spatial neglect') showed no contribution of posterior interhemispheric disconnection to the prediction of acute neglect severity. Moreover, albeit a central brain area (i.e. superior parietal lobule) – advocating for the interhemispheric imbalance model – was detected in this analysis, temporal and frontal nodes contributed to the severity in spatial neglect too. Corbetta and Shulman (2011) suggested that damage to these temporal and frontal brain areas might contribute to an indirect dysfunction of parietal nodes and thus, result in the aforementioned interhemispheric imbalance. However, a considerable number of stroke patients show lateralised attentional biases without clear signs of spatial neglect (Vandenberghe et al., 2012), arguing that the pathophysiological mechanism in spatial neglect is not strictly attentional. Altogether evidence from behavioural as well as from neuroimaging studies condensate to the conclusion that the imbalance model might be far from being complete, as it doesn´t address fully the egocentric core bias in spatial neglect.

A further attentional model, compatible with the aforementioned imbalance hypothesis, was suggested by Posner et al. (1987). The authors argued that the central deficit in spatial neglect patients is an impairment in disengaging attention from current hot spots in the ipsilesional scenery towards contralesional targets (Posner and Driver, 1992). However, spatial neglect patients are able to perform top-down directed movements in all directions without any directional preference (Husain et al., 2001; for review see Karnath, 2015; Machner et al., 2012; Niemeier and Karnath, 2000; Ptak et al., 2009). This model is probably the consequence of a missing differentiation between the terms 'spatial neglect' and 'extinction', which, after being used interchangeably or after considering spatial neglect as a more pronounced form of extinction, are now mostly considered as distinct deficits (for discussion, see Karnath and Rorden, 2012). Moreover, from a neuroscientific perspective, the egocentric core symptoms in spatial neglect might occur together with deficiencies in attentional disengagement and shifting, as they may arise from damage to neighbouring brain areas. Thus, these behavioural phenomena might not systematically reflect the same pathophysiological process. For detailed discussions I refer to the appended projects.

3.2 Representational Models

The main idea of representational models of spatial neglect is that these patients suffer from a deficit in the mental representation of space. Support for this idea comes from well-known experiments, where patients were asked to either verbally report items of

an imagined scenery (Bisiach et al., 1979) or to draw something they previously memorised. Typically, spatial neglect patients are not able to describe content of the contralesional side of the space based on the vantage point relative to their egocentric perspective. However, when patients are instructed to shift their vantage point to the contralesional side, they are suddenly able to report items they missed before. The authors of the investigation suggested that the mental representation of the contralesional side of space might be deficient in spatial neglect patients. Similar findings were reported in further studies (Bartolomeo et al., 1994; Bisiach et al., 1981; Ogden, 1985; Rode et al., 2004, 1998). Generally, it was suggested that processes which lead to spatial attentional deficits in mental imagery and mental representation might also lead to deficits in the real external world (Bartolomeo, 2002; Bartolomeo et al., 2005; Rode et al., 2004) and hence, call for a common model. It was suggested that spatial neglect might arise due to amputation (Bisiach et al., 1994) or distortion (Bisiach et al., 1996) at the level of mental representations. Bisiach et al. (1996) interpreted their findings as an anisometric horizontal bias (Bisiach et al., 1996), leading to contralesional expansion and ipsilesional compression of the spatial representation in neglect patients. Further ideas were formulated, for example, a linear compression of spatial representations to the ipsilesional side (Halligan and Marshall, 1991) or a lack of contralesional attentional exploration (Bartolomeo et al., 2005). It is important to note that these assumptions were mainly based on results from the line bisection task. By using more sophisticated experimental designs, these ideas could not be experimentally confirmed in or exclusively related to spatial neglect patients (Doricchi and Angelelli, 1999; Ferber and Karnath, 2001b; Karnath and Ferber, 1999). Recently, it was suggested that scores in spatial imagery tasks can be related to SWM deficits and thus, SWM could be a promising candidate to explain representational findings (Wansard et al., 2016). Wansard et al. (2016) were able to predict significantly the performance in a spatial imagery task by SWM skills, showing, that the occurrence of representational neglect increases when SWM is impaired. However, the same pattern was observed in healthy participants and thus challenges the view that SWM deficits are part of the core pathology of spatial neglect. As to date, there are only few accounts for this idea and more studies are needed to evaluate the role of SWM in representational models of spatial neglect and spatial exploration.

3.3 Transformational Models

Transformational models are based on the idea that the transformation of input information from different peripheral sources (i.e. eye muscle proprioception, eye-in-space and eye-in-head position, efference copy, vestibular input and neck muscle proprioception, auditory input, retinotopic and head-centred coordinates of the visual space) into an integrative representation of the body in space is systematically biased in spatial neglect patients. Indeed, several studies show that spatial neglect patients reorient themselves to a new egocentric 'default' position, as it was shown by the displacement of eye-in-head and head-on-trunk orientations (Becker and Karnath, 2010; Fruhmann-Berger and Karnath, 2005). In general, the systematic error in coordinate integration results in a rotation of the whole egocentric reference system around the patients´ earth-vertical body axis to a new ipsilesional 'default' position (Karnath, 2015, 1997) which is the starting point for spatial orientation, space exploration, and determination of egocentric body position in space. Indeed, if we consider the distribution of the search pattern in spatial neglect patients, we see, that the bell shaped pattern is not skewed to the ipsilesional side, as it would be predicted by the aforementioned attentional models, but the whole pattern is shifted to the ipsilesional side, keeping the original exploratory bell shape (Karnath, 1997; Karnath et al., 1998). Besides the general horizontal shift, the exploration pattern does not differ much from to the one from healthy subjects. Evidence that the brain uses internal maps of the visual environment and thus relies on coordinate integration from different sensory modalities comes additionally from neuropsychological findings in monkeys and neuroimaging/psychophysical studies in human subjects (Andersen et al., 1997, 1993; Bottini et al., 2001; Boussaoud and Bremmer, 1999; Brotchie et al., 1995; Chen et al., 2012, 2014; Frankenstein et al., 2012; Galletti et al., 1993; Saj et al., 2014; Schindler and Bartels, 2013; Snyder et al., 1998) and from complex computational models of spatial neglect (Parr and Friston, 2018).

Hence, by experimentally manipulating afferent signals it is possible to reorient the visual scan path in neglect patients and even in healthy participants, as it was shown with neck proprioceptive or vestibular stimulation (Karnath et al., 1996). Neglect patients do not only show egocentric biases but might also have deficits in object-based coding. Recent findings also show that egocentric and allocentric coding both coexist and are interacting with each other (Karnath et al., 2011; Li et al., 2014; Rorden et al.,

2012b). To account for these two types of coding, the initial transformation model for the visual modality can be extended by the so-called 'integrated space-object map' (ISO-map), introduced by Niemeier and Karnath (2002). Following these authors, the position of an object will be coded in head- and/or trunk-centred coordinates (egocentric) simultaneously to a within-object based type of coding (allocentric). The ISO-map extension assumes that in neglect patients with right brain damage, salience functions will be biased within the typical bell-shaped exploration path monotonically from left (contralesional) to right (ipsilesional) for egocentric coding. This is combined with a lateral gradient for object-based allocentric coding. In practical terms, this means that the likelihood to perceive left sided features of an object will increase the more the position of the object shifts to the ipsilesional side of the space.

Finally, Karnath (2015) suggested that a combination of a modified version of the interhemispheric attentional rivalry model and the transformation model might be valuable to address experimental observations in spatial neglect. Following the author, it is possible that the matrix (i.e. altered representation of own body position with respect to external objects) on top of which top-down control of spatial attention (i.e. voluntary shifts of spatial attention) are executed appears to be disturbed in neglect patients. This, however, requires a conceptual change in attentional models from neglect as an attentional (directional) to neglect as a body-centred syndrome.

From a neuroanatomical perspective the transformation model raises the question if there are crucial nodes playing a central role in the multimodal integration of sensory information. Karnath et al. (2001) suggested the right insula, superior temporal cortex and temporo-parietal junction as key candidates as they consist of multimodal cell populations receiving information from various sources. Despite that these areas are repeatedly detected in studies using voxel-based lesion-behaviour mapping, a clear disclosure on their role in the development of spatial neglect is still not possible.

4 Lesion-deficit inference – the engine of modern neuropsychological research

In the following section, I give a short historical introduction on milestones in the research of spatial neglect and especially the neuroanatomical basis of the syndrome.

Moreover, I want to recapitulate crucial methodological developments which allowed to consecutively accumulate insights on lesion-behaviour associations, and which are the precursors of techniques employed in the present thesis. However, I will not provide a detailed overview about anatomical findings in spatial neglect and refer the interested reader to the appended projects.

4.1 Historical Landmarks

After the well-known descriptions of the aphasic patient Louis Victor Leborgne in 1861 by Paul Broca, research of cognitive functions changed dramatically. The patient he described was only able to produce the syllable "tan", a behaviour which could be related to a lesion in the left inferior frontal cortex by performing post-mortem autopsy. Later this finding could be replicated with the same technique many times. At that time the functional anatomy of the brain could only be studied by focusing on single cases, (i.e. single cases of patients with brain damage). According to Halligan and Marshall (1993), the first description of the disorder of spatial neglect with reference to the neuroanatomical basis was provided only a few years later by Hughlings Jackson in 1876. After presenting his patient a task to test visual acuity, he noted "… [the patient] began to read at the lower right corner and read backwards" and that the patient had also difficulties in reading letters on the left side of words. He concluded that this behaviour was related to a posterior temporal lesion in the brain of that patient. Thus, he provided first evidence for his two year earlier postulated hypothesis in 1874 that visuo-spatial tasks might be processed predominantly in the right hemisphere. In the years that followed, many single case descriptions related to a variety of visuo-spatial and attentional symptoms were reported by neurologists and gathered a lot of attention in the research community. However, these symptoms were not all intrinsically related to what we define nowadays as spatial neglect. After these early case descriptions and during a second historical period that followed, much effort was made to focus on case series and to conduct group studies. The goal was mainly to define and distinguish different disorders of visual and spatial attention and to operationalise clinical tests. This period was especially driven by the consequences of the first (e.g. investigations by Holmes and Lister [1916]; Poppelreuter [1917]) and second (e.g. investigations by Brain [1941]; Paterson and Zangwill [1944]) world wars, but also the Chinese and Russian-Japanese (e.g. investigations by Inouye [1909]) wars. Hence, neurologists where confronted with a large number of young soldiers with non-lethal gunshots and

relatively discrete brain damage. These patients where specifically suited to participate in group studies. Concurrently, a second method to investigate brain-function relationships became available. Holmes and Lister (1916), in a same way as Inouye (1909) examined entry and exit wounds in the skull and were able to map the primary visual cortex in-vivo and with high precision using cranio- topic measurements of the bullet's locations. Nevertheless, post-mortem dissections stayed the standard procedure during that time, as they provide a direct way to characterise brain lesions.

A huge step forward in the investigation of brain-function relationships was marked in 1971, when the first in vivo x-ray computed tomography scan of a human brain was performed. The development and consecutive implementation of x-ray based computer tomography (CT) (Godfrey Hounsfield, 1972) and magnetic resonance imaging (MRI) (Lauterbur, 1974, 1973) had dramatical consequences for clinicians and researchers at that time, as it was now possible to obtain in-vivo images in living organisms. In stroke diagnosis and treatment, MRI and CT imaging became widely available and are nowadays part of the clinical routine on admission if a patient shows clinical signs for stroke.

4.2 Neuroimaging in neuropsychology: from descriptive reports to advanced statistical modelling

Anatomical information collected with these new brain-imaging techniques were also used in research and thus, almost 10 years after their introduction, Heilman and colleagues (1983) conducted one of the first modern anatomo-behavioural studies in 10 patients presenting clinical signs of spatial neglect. The study was conducted to delineate the neural correlates responsible for the development of the syndrome. The authors used a lesion overlap method, which became quite prominent at that time. In general, CT scans of patients were visually inspected, and the individual anatomy and lesion location were evaluated by experienced neuroradiologists or scientists. In a second step, lesions were transferred (i.e. drawn) manually onto a brain template with more or less anatomical landmarks. Finally, the lesion of each patient participating in the study was mapped onto the template producing an overlap plot of all lesions. Using this technique, it was able to get qualitative information about brain areas that are more often affected than others in a patient group presenting a discrete syndrome. For spatial neglect, Heilman and colleagues (1983) found that lesions centred on the inferior parietal lobule and the temporo-parietal junction were representative for the patient

sample. A few years later, Vallar and Perani (1986) used the same method in a much larger group of 47 right hemisphere stroke patients with signs of spatial neglect and found multiple distinct patterns by inspecting their lesion overlap plots. The lesions of several patients centred on perisylvian structures, whereas the lesions of other patients centred on the parieto-occipital junction or the supramarginal gyrus of the inferior parietal lobule.

Although the lesion overlap procedure can be classified as having had large impacts on the investigation of lesion-behaviour relationships, Rorden and Karnath (2004) noted severe limitations. Most importantly they discussed that this overlap method does not allow to distinguish between brain regions that are particularly vulnerable to injury and the neural correlates of the behavioural pathology. Hence, by using this technique in spatial neglect, we cannot differentiate if reported´ areas are specifically related to the syndrome or if local overlap maxima only reflect frequently occurring damage in stroke patients (Sperber and Karnath, 2016b). To address this limitation, Rorden and Karnath (2004) argued in their review to perform subtraction analysis by: (i) collecting data from two groups, patients with brain damage having a specific symptom and patients with brain damage not having the symptom, (ii) deriving topographical overlaps for each of the groups and (iii) now contrasting these overlaps with one another. Although this method is still a descriptive technique, it allows to reveal areas of the brain which are damaged specifically in stroke patients with the disorder compared to stroke patients without the behavioural pathology of interest. Actually, this technique was not completely new, as Binder and colleagues (1992) applied the principle of the subtraction analysis several years ago to investigate the anatomical basis of spatial neglect. They were also one of the first groups showing that there might be differences in anatomical findings with respect to the clinical task used for detecting spatial neglect (see chapter *'2.4 Diagnostic procedures to detect lateralised spatial biases after stroke'* for this discussion).

With new technical progress, digital brain scans became more and more available and allowed to process scans directly using several software packages and appropriate hardware. Hence, it was now possible to produce overlap and subtraction plots without transcribing lesions manually slice by slice to a separate sheet. By working directly on digital scans in a 3D voxel space (voxel = volumetric pixel) quantitative evaluation and statistical inference in lesion-behaviour mapping became possible notably through the development of tools like BrainVox (Frank et al., 1997)

or voxel-based lesion-symptom mapping (VLSM; Bates et al., 2003). Thus, after the era of relatively 'simple' lesion overlap plots and subtraction analyses, a completely new world of statistical applications allowing inference in stroke populations – based on non-invasive imaging – became available.

4.3 Methodological considerations in pre-processing of lesion data

Although these tools became very popular among research groups interested in mapping lesion-behaviour correlates, they could not be used directly with individual clinical MRI or CT scans in the native patient space. Moreover, there are several parameters depending on individual choices which can influence outcomes of statistical analyses, and which should be selected with precaution. In the following paragraph, I will not go through every methodological detail, as this would be out of scope of the present thesis. In contrast, I provide an overview about the most important steps to conduct modern voxel-based lesion-behaviour mapping analyses. For any reader who is interested in further details, I refer to the review by de Haan and Karnath (2018) and to a recently published book chapter (Karnath et al., 2019), where I contributed to a detailed pre-processing and analysis pipeline.

First, it is important to highlight that clinical scans generally do contain contrast information about different tissue types. It is for example possible not only to distinguish between grey and white matter tissue, but also to uncover different pathological processes, like bleedings, infarction or tumours. To be able to work with brain lesions, the exact borders and extent of brain damage needs to be delineated and extracted before any lesion-deficit method can be applied. Choices on lesion visualisation and lesion demarcation are not trivial (for reviews, see Merino and Warach, 2010; Provenzale et al., 2003) and decisions on scan-modality and the consecutive delineation procedure will have an impact on the quality of the outcome. The ability to visualise the full extent of brain damage varies as a function of time since stroke onset and scan modality (i.e. most importantly: T2FLAIR MRI, Diffusion MRI, Non-contrast CT). In most cases clinicians or researches are confronted with a multitude of sequences and image files and need to decide which one to use with respect to study aims and stroke characteristics (i.e. hyperacute, acute or chronic phase after stroke onset, haemorrhagic or ischemic stroke, small or large extension of damage, low or high resolution).

After visualisation of the damage, it is necessary to delineate and extract the 3D lesion information which is part of the image. Several procedures were suggested. One of the oldest techniques is the manual demarcation of the lesion, slice-by-slice, which can be done directly in most software packages. These packages are also able to visualise scans with different modalities. Although this procedure is time consuming, can be observer-dependent (Ashton et al., 2003) and needs expert knowledge on the typical presentation of a brain lesion, it outperforms fully-automated methods in precision. Therefore the manual demarcation can be considered as the 'gold-standard' (see de Haan and Karnath, 2018). Nevertheless, compromises between manual and automatic lesion delineation exist in terms of semi-automatic approaches (e.g. Clusterize Toolbox: de Haan et al., 2015). Choices on lesion demarcation are crucial, because a poor delineation might produce false-negative or false-positive results, as shown by Pustina et al. (2016). After successful delineation, an individual binary (i.e. 0 = no damage and 1 = damage) 3D lesion map can be extracted for each patient.

At this point most researchers aiming to conduct a group study are confronted with the problem that patients´ skull and brain differ in their morphometry and there can be large variations between patients in the exact positioning on the MRI or CT bed. What follows is that these brains and the thoroughly delineated lesions from the previous step are not in the same coordinate space. This means that the coordinates of a specific area in one patient might be located 'miles' away from the coordinates of the same area in another patient. Keeping this in mind, overlap plots and subtraction analysis on the one side, but also advanced statistical analyses on the other side cannot easily be performed and a further pre-processing step is needed. It is important to note that this is not a problem of lesion-behaviour mapping alone, but it is rather a general issue in neuroimaging research. To solve this issue, lesion maps need to be transferred to a common reference space. In former days, this was done by manually transferring the lesioned area of each individual patient to a template sheet of a brain sketch (as in Binder et al., 1992) or in digital times on a digital brain template. However, this required a lot of neuroradiological and anatomical expert knowledge to achieve acceptable results and it was extremely time consuming. A more elegant and feasible approach is called normalisation. During the normalisation process, the 3D brain of each patient and the corresponding lesion map are transformed linearly (i.e. by affine) and non-linearly (i.e. non-affine) by warping them into a common standard stereotaxic space and minimizing the least mean square differences between the voxels of the individual

brain and the template image (Ashburner and Friston, 2003). The choice of the template to normalise to is not trivial and should have the same image modality as the patient scan to achieve acceptable results. Especially for elderly stroke patients age-specific templates were created to maximise robustness of the normalisation process (Rorden et al., 2012a). These templates were also used in the appended studies of the present thesis. After applying the normalisation step to each and every lesion and visually inspecting the result, it is possible to proceed to perform statistics.

4.4 From univariate to multivariate lesion-behaviour mapping

Statistical protocols which dominated the field for almost 2 decades were largely based on univariate testing as in voxel-based lesion-symptom/behaviour mapping (VLSM/VLBM). This means that for every voxel, one statistical model is fitted and statistically tested. In a three-dimensional brain image matrix of 181x217x181 1mm³ voxels, this means that theoretically 8.562.386 statistical tests are computed, and that inference is given for each single voxel. Therefore, this approach is also classified as 'mass-univariate'. After lesion overlap and subtraction plots were the dominant procedures in the field, most of the studies aiming to detect the anatomical correlates of spatial neglect were employing this new protocol. Nevertheless, there are several drawbacks with this procedure. Some of them are related to neuroimaging studies using the same theoretical framework (i.e. in general all neuroimaging studies employing univariate approaches), others are specific to voxel-based lesion-behaviour mapping.

One huge problem is that this approach assumes that information in each voxel is independent from information in every other voxel. However, this cannot be assumed in the human brain as the extent of lesions follow systematic principles (Sperber and Karnath, 2016b) (e.g. the vasculature of the brain). Moreover, from a theoretical perspective if one single voxel of 1mm³ passes the significance threshold, what is the ecological value of such a single finding? Actually, it is already more likely, that other voxels pass the threshold, too, solely based on their neighbourhood to another significant voxel.

Generally, we grant our analyses a certain error probability (α-error or α-level), as statistics in most cases do not provide 100% precision. As the probability of making an α-error (i.e. to detect signal in the data which in reality is not there) is directly linked to statistical power and the ability to detect a significant association between dependent and independent variables, this rate needs to be chosen with precaution. If the threshold

for the acceptable error is very low, we might be too liberal and end up with a huge number of false positive results and we are committing a so-called Type-I error (i.e. we reject the null-hypothesis and we assume that there is true signal in the data). However, if the error probability is too high, we might be too conservative and perform a Type-II error (i.e. we are going to accept the null-hypothesis and reject true findings). In lesion-behaviour mapping, thresholds for the α-level are generally defined as 0.05 or 0.01.

As we are performing a huge number of statistical tests, we are further running into a multiple comparison problem because we are theoretically increasing the probability of performing an α-error by performing one statistical test in each voxel. To illustrate this with the aforementioned numbers and an α-level of 0.05: If the data matrix consists of 181x217x181 = 8.562.386 voxels, then 8.562.386 x 0.05 ~= 428.119 voxels will randomly become significant, although there is no true signal. Fortunately, several procedures were developed to control for this issue. Typical procedures include family-wise error correction (FWE) or false discovery rate correction (FDR; Benjamini and Yekutieli, 2001). Whereas FDR controls the proportion of false positives amongst observed positives, FWE controls for the probability of observing a single false positive. Multiple comparison control by FDR means that with an α-level of 0.05, up to 5% of the observed positives might be false positives. If there are no positive findings in the results, this procedure is as conservative as the Bonferroni correction (see below). However, with an increasing number of positives in the data, FDR will be more liberal. The simplest way of controlling the FWE rate is called Bonferroni correction. As Bonferroni correction, however, can be extremely conservative (i.e. dividing the α-level by the number of statistical tests performed in one analysis) in neuroimaging studies other variants of FWE control were suggested, as, for example, the assumption free permutation-based FWE correction (Nichols and Hayasaka, 2003; Nichols and Holmes, 2002) which was defined as 'gold-standard' in univariate VLBM (de Haan and Karnath, 2018). Permutation testing for statistical inference in general provides a computationally intensive but extremely useful framework (Mirman et al., 2018). It doesn´t rely on any distributional assumptions and is straight forward. First, for each permutation a test statistic is drawn from the real dataset. Secondly, pseudo-data is generated by shuffling patient labels and scores to create a random distribution. A second test-statistic is drawn from this pseudo-data and compared to the initial value from the first step. This is generally done for a large number of permutations (i.e. 5000-10000). We count the iterations, where the test-statistic of the real label-score

combination is higher than the test-statistic of the permuted (i.e. shuffled) data, derive the probability value and compare it to the a priori defined threshold (i.e. 0.05, 0.01…). It is important to note, that in most cases, the distribution created through permutations is not 'exact', as it is generally approximated. For this approach to be exact, it is necessary to perform a permutation for each possible label-score combination, which is computationally not (yet) feasible. For a large amount of datapoints, as in VLBM, we typically derive one maximum test-statistic over all voxels (instead of one test-statistic for each individual voxel) obtained in each permutation. To summarise, permutation testing is simply evaluating if the brain-behaviour association in our real dataset is significantly different to the brain-behaviour association in a randomly generated pseudo-dataset.

A further issue in lesion-behaviour mapping is that if damage in multiple areas of the brain are leading to the same symptom, these areas might be considered as counterexamples for each other which undermines statistical power (i.e. 'partial injury problem'; Kinkingnéhun et al., 2007; Rorden et al., 2009). As a statistical test is performed in each isolated voxel, the status of other voxels is not considered in the analysis. In extreme cases this violation of statistical independence can lead to a spatial bias of the resulting statistical map in VLBM (Inoue et al., 2014; Mah et al., 2014). Although the spatial bias can be reduced by the implementation of correction factors, such as lesion volume control or sufficient lesion affection (Sperber and Karnath, 2017), it cannot be completely resolved. These correction factors are in fact not new, as they were introduced for VLBM several years ago. Lesion volume control is thought to control for biases induced by large lesions. As larger lesions are in general related to a more severe behavioural deficit, lesion volume is typically considered as nuisance covariate. To avoid that lesion-behaviour mapping identifies areas of the brain related to behaviour and not simply to lesion size, several procedures to account for it were suggested, including nuisance regression of the volume effects out of behaviour, voxel status or both (see DeMarco and Turkeltaub, 2018; Karnath et al., 2004; Schwartz et al., 2012) and direct total lesion volume control (dTLVC; Zhang et al., 2014). Another strategy can be to restrict the analysis to only patients with small lesions (Price et al., 2017), although this can produce further issues related to statistical power, as most areas of the brain will typically not be represented in the analysis. In practical terms, the analysis algorithm will not be able to detect any common anatomical pattern due to high variability in lesion configurations throughout the sample. Further, the application

of a minimum lesion affection criterion was recommended to exclude single spurious voxels that might bias findings. Choices on these parameters are not trivial. A practical illustration, how these factors and different strategies for multiple comparison control can affect the analysis outcome is shown in the appended project one: '*Using machine learning-based lesion behavior mapping to identify anatomical networks of cognitive dysfunction: Spatial neglect and attention*'.

Although all these approaches in lesion-behaviour mapping made a considerable impact to the research of anatomo-behavioural associations and pushed the elaboration of theoretical models for various neurological syndromes, they were recently challenged.

After the study from Mah et al. (2014), showing for the first time the presence of a spatial bias in VLBM data, a general and rather critical discussion about the validity of mass-univariate lesion-behaviour mapping intimidated the field. As the authors directly compared univariate and multivariate techniques to each other, they emphasised, however, the benefits of multivariate lesion-behaviour mapping (MLBM) and strongly recommended a general transition to new approaches to overcome the aforementioned issues in mass-univariate VLBM. At nearly the same time, first studies started to implement multivariate algorithms to model lesion data. The first analysis protocols were quite computationally intense and often restricted to the analysis of only a few larger defined regions of interest at once (Smith et al., 2013). A huge impact on the whole research field was made by the publication of Zhang et al. in 2014. The authors used a similar mathematical approach as Mah and colleagues (2014), based on support vector machines (SVM; Drucker et al., 1996; Vapnik, 1995), and found a way to easily extract and statistically test feature weights (i.e. 1 weight per voxel location), a considerable innovation. Moreover, the authors developed and distributed a toolbox of analysis scripts, which made this highly complex technique available to a broader public (https://github.com/yongsheng-zhang/SVR-LSM). Finally, the authors did not only demonstrate how to model continuous behavioural data with Support Vector Regression (SVR; Cortes and Vapnik, 1995) on a whole-brain voxel-wise level, but also validated the technique empirically using simulations. Interestingly, results of their simulations were very promising, as they detected a clear superiority of their MLBM method compared to VLBM, especially when a complex network is the target. The approach was labelled as Support Vector Regression based Lesion Symptom Mapping (SVR-LSM) and quickly became popular (Chen et al., 2018; DeMarco and Turkeltaub,

2018; Fama et al., 2017; Ghaleh et al., 2018; Griffis et al., 2017b, 2017a; Lacey et al., 2017; Mirman et al., 2015; Skipper-Kallal et al., 2017; Sperber et al., 2019a; Xing et al., 2016; Zhao et al., 2018). In the last few days, more and more scientists in the field performed a transition to MLBM machine-learning based techniques. I adopted this method and implemented variations of the initial scripts not only to conduct projects in spatial neglect, but also to use it in stroke patients suffering from aphasia or apraxia (Sperber et al., 2019a). Moreover, I contributed to the methodological validation of the technique (Sperber et al., 2019b), which allowed us to rule out some myths concerning, for example, the systematic misplacement of anatomical findings or the necessity of multiple comparison corrections. In the present section, I will not go into more detail about the SVR-LSM method, but I refer to the introductory and comprehensive work of Zhang et al. (2014) and the method sections of the appended projects.

In the last few years, new methods for the evaluation of remote structural and functional effects of focal brain damage in the investigation of lesion-behaviour relationships were developed. These techniques and tools include, for example, lesion network mapping (Boes et al., 2015), disconnection symptom mapping (Foulon et al., 2018; Kuceyeski et al., 2013) and connectome lesion-symptom mapping (Del Gaizo et al., 2017; Yourganov et al., 2016). The benefit of these techniques is that they refer to large databases of normative neuroimaging data to approximate effects real lesions might have on structural and functional network dynamics, and thus are able to complement research in the field of lesion-symptom mapping (Karnath et al., 2018). Combined with multivariate analysis protocols (e.g. SVR), these methods help to approximate step-by-step the high-dimensional structure and complexity in lesion data.

4.5 Many years of lesion-behaviour mapping research in spatial neglect – Why starting all-over again with multivariate approaches?

It is important to note, that it took many years and a large number of studies using VLBM and MLBM techniques to be able to formulate methodological guidelines at the present stage. In the meanwhile, methodological choices in lesion-behaviour mapping in spatial neglect were not always based on a general agreement between research groups, which had an impact on the study outcomes and anatomical findings. As studies varied largely in experimenters' choices and did rarely engage in replicational designs, findings were discussed controversially. After a while, by aggregating all these study outcomes together, the picture of a large right hemispheric network in spatial attention

and neglect was drawn. However, a lot of these studies were constrained by several limitations, which made it hard to interpret the results in its entirety. In the next paragraph I give a short (i.e. not exhaustive) overview of several typical methodological considerations, when reading publications in spatial neglect or VLBM/MLBM research. I hope to be able to sensitise the reader for an informed and comprehensive evaluation when reading these investigations. Please note that beside the factors I am going to highlight below, these studies varied also considerably in the diagnostic procedures for spatial neglect (see chapter *'2.4 Diagnostic procedures to detect lateralised spatial biases after stroke'* for a discussion), which further contributed to heterogeneous results.

In Karnath et al. (2011b) and Rorden et al. (2007) results seem to show at first sight indeed large parts of the spatial neglect network as suggested before, but the authors did, for example, not control for lesion volume effects. The significant signal in their data rather shows one big cluster which seem to spill over the tested area. Similar to what was recently reported by Pustina et al. (2018), it is possible that parts of the resulting topography is related to the effect of a lesion volume confound. Indeed, also the study by Zhang et al. (2014) shows that the Receiver Operator Characteristic without any lesion volume control is inferior (for multivariate as well as for univariate mapping) to analyses with lesion volume control. This leads to an increase of false positive findings (far away from the true 'ground truth' areas in their simulations). In a study by Chechlacz et al. (2012), who employed an Activation Likelihood Estimation (ALE) meta-analytic approach, findings were exclusively based on former univariate investigations, including those with several methodological caveats. Another study by Chechlacz et al. (2010) detected large parts of the presumed network by following a multi-imaging and multimethod strategy (Voxel-Based Morphometry, Voxel-Based Lesion-Symptom Mapping and Diffusion Tensor Imaging), but similar as for Karnath et al. (2011b), without lesion volume control (for VLBM). Moreover, the inclusion of a variety of behavioural covariates and the different findings for allocentric vs. egocentric neglect symptoms make it difficult to interpret the findings directly and solely in relation to the aforementioned core symptoms in spatial neglect. Thiebaut de Schotten et al. (2014) reported only results uncorrected for multiple comparisons for their 'voxel-wise topological lesion-deficit analysis', providing a rather descriptive evaluation of the data. The authors conducted also a traditional VLBM control-group analysis which showed a similar pattern as in previous investigations (Chechlacz et al.,

2010; Karnath et al., 2011b). Although a multiple comparisons correction was applied, the authors decided to perform no lesion volume correction. Hence, very much of the media territory and cortical structures at its borders passed the threshold. Interestingly, this pattern is very similar to the univariate analysis without lesion volume control but with FDR correction for multiple comparisons of Fig. 5 in the appended project one: *'Using machine learning-based lesion behavior mapping to identify anatomical networks of cognitive dysfunction: Spatial neglect and attention'*. However, it is rather unlikely that each and every lesion within the media territory leads to spatial neglect. Umarova et al. (2016) showed results without correction for multiple comparisons. They even stated that "after application of the false discovery rate (FDR) correction for multiple comparisons ($p < 0.05$ after FDR) no significant difference was found between groups".

From these analyses it seems that the controversial discussion in the literature was rather based on methodological choices than valid anatomical results. This, however, is not only true for univariate investigations, but also for the first multivariate studies.

In one of the first MLBM analyses by Smith et al. (2013), single parts of the presumed network were reported as contributing most to the classification between spatial neglect and control patients (mainly the superior temporal gyrus). The authors restricted their analysis a priori to only a limited set of regions of interest (2 or three at once), although multiple sub-analyses of 2 or 3 regions of interest might provide redundant information. Keeping this in mind, the procedure is by definition not able to map multiple areas involved within large-scale networks in a single analysis. Corbetta et al. (2015) pointed in their investigation to limitations based on insufficient lesion overlap of some areas, which affects the ridge regression performance. Similarly, in another investigation, the authors restricted the analysis to solely right MCA territories and thus they reduced the set of detectable areas a priori, i.e. the analysis was based on a preselected subset of right hemisphere stroke patients not necessarily corresponding to the whole unselected population (Carter et al., 2017). Although their analysis was restricted to the MCA territory, they surprisingly detected no temporal cortical involvement in spatial neglect, which seems to be crucial in the development of the syndrome (Karnath and Rorden, 2012). In Ramsey et al. (2017), attentional deficits were operationalised as a compound score of spatial and non-spatial tasks by performing a principle component analysis (PCA). A drawback of PCA in delineating

lesion components and to relate that as a single predictor to a behavioural symptom is a loss of spatial specificity compared to voxel-wise analyses. Although PCA approaches are in general able to detect coarse-grained explanatory variables, there are some limitations which affect the outcome (i.e. selection of an arbitrary criterion for component extraction, which ignores unexplained variance when selecting a limited number of components and which necessitates subjective a posteriori interpretations).

Despite the methodological caveats I summarised in the present section, I want to clarify that I do not aim to challenge methodological decisions in previous works on the anatomical network of spatial neglect. In fact, I rather think that we need all these multi-modal and multi-method designs with dissimilar patient-samples to be able to address the complexity and high-dimensionality in lesion data, as introduced by Mah et al. (2014) and recently comprehensively discussed by Sperber (2020). In general, univariate VLBM might be able to perform as good as MLBM, if several prerequisites are fulfilled - as it was demonstrated in a clinical example on Fig. 4 in my first thesis project: '*Using machine learning-based lesion behavior mapping to identify anatomical networks of cognitive dysfunction: Spatial neglect and attention'* -. However, albeit methods might complement each other (Ivanova et al., 2020), univariate VLBM will never be able to address the higher dimensionality in lesion data and hence the transition to multivariate analysis protocols will become mandatory. Nevertheless, also a single multivariate study – at least with respect to the state-of-the-art methods at hand – will be unable to come to causal conclusions and we need all these different ways of approaching a same problem to condensate findings to a bigger coherent and complex picture, allowing us to formulate new and complement old theories.

5 Empirical research questions in my thesis

5.1 Using machine learning-based lesion behavior mapping to identify anatomical networks of cognitive dysfunction: Spatial neglect and attention

The first empirical work applies a new MLBM algorithm, SVR-LSM, to a large set of 203 right hemispheric stroke patients to delineate the neural correlates of the core symptoms of spatial neglect. Previous studies primarily focused on univariate statistics (i.e. VLBM) leading to inconsistent results and controversies, which can be explained to some extend by methodological caveats of the univariate method. Although the idea of a wide-spread network that might underlie spatial orientation and neglect was suggested previously in the field, one single study confirming this was still lacking. Moreover, in most of the former lesion-behaviour mapping studies, either univariate or multivariate techniques were employed, and the latter studies stated their pre-eminence without any empirical verification. Direct comparisons between both methods in real patient samples and beyond simulations were lacking. The results of the present work indeed confirm the presence of a complex right hemispheric network in spatial neglect. Surprisingly, a similar topographical result can in general be detected regardless of the statistical analysis technique (i.e. VLBM or MLBM). Nevertheless, in terms of severity prediction and evaluation of model performance, the SVR-LSM technique shows it´s superiority. Specifically, the multivariate technique allows an evaluation of the anatomo-behavioural model as a whole, compared to the VLBM approach, which generates one model per voxel unit.

5.2 Structural (Dis)Connectomics of spatial exploration and attention: a study of stroke patients with spatial neglect

In the first empirical work, I focused especially on focal brain damage related to spatial neglect. Therefore, results are limited to areas directly affected by the lesion itself. Previous findings come to the conclusion that brain lesions do not only produce local damage, but also remote disconnection or dysfunction. To be able to delineate these areas, several new techniques were suggested, as for example disconnection-symptom mapping (Foulon et al., 2018; Kuceyeski et al., 2013), connectome lesion-symptom mapping (Del Gaizo et al., 2017; Yourganov et al., 2016) and lesion-network mapping (Boes et al., 2015). These techniques are particularly suited to delineate distant areas of

the brain which are functionally or structurally affected by focal lesions. As it is very hard to collect functional MRI or diffusion MRI data directly in clinical populations, these techniques use indirect but elegant procedures for estimating structural or functional disconnection. In the second empirical work, I aim to focus on the structural (dis)connectome in stroke patients and by that complement findings of the first project. To do so I elaborate a connectome lesion-symptom mapping analysis protocol based on state-of-the-art pre-processing of diffusion weighted imaging data and use this new approach combined with MLBM (i.e. SVR-CLSM) to detect crucial links and central hubs whose disconnection is related to the syndrome of spatial neglect.

5.3 Disconnection somewhere down the line: Multivariate lesion-symptom mapping of the line bisection error

The third study aims to resolve contradictory anatomical and behavioural findings of the line bisection task, especially with respect to spatial neglect. The line bisection task is frequently used in the diagnosis of spatial neglect, nevertheless its validity was continuously challenged. Although there is partly correspondence between findings in previous anatomical studies, it is not yet possible to find a unifying theory. By using two different multivariate machine-learning based approaches to delineate local damage (i.e. SVR-LSM) and remote disconnection (i.e. SVR-DSM: Support Vector Regression Based Disconnection-Symptom Mapping), the study attempts to depict the configuration of grey and white matter structures related to pathological rightward deviation. To address this question, these analysis protocols are applied to a sample of 163 right hemispheric stroke patients who completed the line bisection task. In this empirical work, I show that the severity of pathological line bisection (i.e. the line bisection error) is related not only to multiple lesion locations, but also to distant intrahemispheric and interhemispheric fibre disconnections, partly corresponding to, but also dissociating from findings in projects one and two.

5.4 Anatomical substrates of visual extinction: A multivariate lesion analysis study in acute stroke

The fourth empirical work investigates the anatomical underpinnings of a pathological behaviour closely related to spatial neglect, namely extinction. Extinction is related to the ability of multi-target attention, i.e. the ability to spot and react to multiple visual targets presented simultaneously across both visual fields. Patients showing extinction

are able to respond to single unilateral targets. However, if targets are presented bilaterally these patients are only able to report the presence of the ipsilesional target. As for spatial neglect and line bisection, previous investigations produced heterogeneous results. By using MLBM in a sample of 108 acute stroke patients, I delineate the full extent of the network associated with visual extinction, which centres around the temporo-parietal junction, confirming previous studies in extinction research.

6 Concluding remarks and future directions

From the first attempts to localise cognitive functions in the brain by dissecting brains post-mortem at the end of the 19th century to advanced statistical and computationally intensive in-vivo approaches which are used nowadays, neuroscientific research in spatial neglect has taken huge steps, initiated by astonishing methodological innovation. Interestingly, the pace of innovation in the field of lesion-behaviour mapping is increasing exponentially. Whereas post-mortem dissection was the standard approach in the field for nearly a century without a particular rival, these days new techniques are going to be redeemed after only a few years and many methodological procedures with similar properties, but individual cost-benefit trade-offs coexist. In my thesis, I showed that modern state-of-the-art in-vivo techniques to model brain-behaviour relationships are able to resolve inconsistencies in the field and close longstanding disputes. In general, results from the appended projects provide valuable information for models of spatial attention and exploration, spatial neglect and associated syndromes. Furthermore, these anatomical findings might guide choices on the design and development of diagnostic procedures and therapeutic interventions.

During my time as a doctoral student, it was important to me to not only apply new 'experimental' lesion-behaviour mapping techniques to neurological syndromes, but also to better understand these methods and to engage in their validation. As the comprehension of these techniques was still in its infancy when I started with my thesis, I contributed to a methodological investigation, showing that issues of spatial displacement and multiple comparisons cannot be completely resolved through MLBM (Sperber et al., 2019b). Right now, I use the methodological insights I gained to apply these new techniques to further neurological diseases. Overall, I would like to deepen my understanding about the high-dimensional structure of lesion-data and use

complementary anatomo-behavioural techniques to refine current insights about the disorder of spatial neglect and associated deficits. One of them is for example lesion-network mapping (Boes et al., 2015), a method which maps the functional network associated with pathological behaviour and damaged remotely through focal lesions. In a similar way as for structural connectome lesion-symptom mapping and disconnection-symptom mapping (see appended project two and three), this method is supposed to allow the indirect evaluation of the functional (dis)connectome based on large databases of normative data. However, as very recently shown by Salvalaggio et al. (2020), it seems that findings from the lesion-network mapping technique, as it was suggested by Boes et al. (2015), do not contribute much to the explanation of variation in the data. By synthesising the functional disconnectome from huge databases of functional imaging data (i.e. neurosynth: https://neurosynth.org), I want to suggest an alternative to the established method, evaluate it from a methodological perspective and apply it to neurological data.

Besides detecting the topography of crucial neuroanatomical damage associated to a behavioural pathology, a new research field is rapidly developing which refers in principle to the same multivariate methods and which can refer to the neuroscientific output from traditional lesion-behaviour mapping studies. In the last few years, the potential of machine-learning based lesion analysis to predict the acute clinical status, or the long-term development and recovery of individual patients attracts more and more interest. The application of the methods I used in the present thesis is not restricted to post-stroke outcome prediction and in many clinical fields, there is an increasing effort to define robust protocols to conduct such predictive analyses. The ultimate goal of these efforts will be to develop simple tools allowing clinicians to enter different type of data (i.e. demographic, genetic, neuroanatomical or behavioural information) about a new admitted patient. An algorithm then produces a report including a diagnostic classification and an evaluation of the severity and course of recovery. Of course, I am talking about a future perspective and there are still many hurdles. However, such a tool will not only answer one of the first questions patients ask: *'When will I recover and what can I do to accelerate recovery'*, but it will also allow clinicians to perform individualised and efficient medicine.

Especially in neurological research, we may ask what parameters and which analysis protocols we need to achieve a decent prediction performance. As discussed in Karnath et al. (2018), anatomical and functional features of acute structural or

functional imaging in the same way as information about lesion location can be useful for predictive models. Although we know already several candidate variables (especially when considering neuroimaging data), we still do not know much – at the present moment – about the optimal way of using that information in the most efficient way. Nevertheless, it was shown that selection of specific features can affect model and prediction performance (Rondina et al., 2016; Yourganov et al., 2015), and thus this knowledge will become crucial. As lesion location can contribute to, but not explain completely the variation in the data, it needs to be combined with many other factors that influence the severity and long-term course of a deficit like age, neuropsychological co-morbity or pre-morbid cognitive status (see Price et al., 2017). In general, machine-learning algorithms used for the aforementioned purposes are not very different from those used in other fields of 'big data' and data mining. However, especially in the clinical domain, innovation is currently mostly restricted by data availability. For translational use, it will be further necessary to detect the most efficient algorithms which maximise prediction accuracy. Right now, I am already collecting patient data to develop long-term predictive models for patients suffering from spatial neglect. To conclude, I hope that my existing and future contributions will be especially useful for clinical applications, as the ultimate goal of neuropsychological research as I see it should be to optimise patient care.

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8 List of papers/manuscripts appended and statement of contributions

Wiesen, D., Sperber, C., Yourganov, G., Rorden, C., & Karnath, H.-O. (2019). Using machine learning-based lesion behavior mapping to identify anatomical networks of cognitive dysfunction: Spatial neglect and attention. ***NeuroImage***, *201*(July), 116000. https://doi.org/10.1016/j.neuroimage.2019.07.013

Daniel Wiesen: Conceptualisation, Formal analysis, Methodology, Investigation, Writing - original draft. Christoph Sperber: Conceptualisation, Formal analysis, Methodology, Investigation, Writing - original draft. Grigori Yourganov: Formal analysis, Methodology, Writing - review & editing. Christopher Rorden: Conceptualisation, Methodology, Writing - review & editing. Hans-Otto Karnath: Conceptualisation, Methodology, Writing - original draft.

Wiesen, D., Bonilha, L., Rorden, C., Karnath, H.-O. (in preparation). Structural (Dis)Connectomics of spatial exploration and attention: a study of stroke patients with spatial neglect.

Daniel Wiesen: Conceptualisation, Formal analysis, Methodology, Investigation, Writing - original draft. Leo Bonilha: Conceptualisation, Methodology, Writing - review & editing. Christopher Rorden: Conceptualisation, Methodology, Writing - review & editing. Hans-Otto Karnath: Conceptualisation, Methodology, Writing - original draft.

Wiesen, D., Karnath, H. O., & Sperber, C. (2020). Disconnection somewhere down the line: Multivariate lesion-symptom mapping of the line bisection error. ***Cortex***, *133*, 120–132. https://doi.org/10.1016/j.cortex.2020.09.012

Daniel Wiesen: Conceptualisation, Writing - original draft, Formal analysis, Methodology, Investigation. Hans-Otto Karnath: Conceptualisation, Writing - review & editing. Christoph Sperber: Conceptualisation, Writing - original draft, Methodology, Investigation.

Sperber, C., **Wiesen, D.**, Karnath, H.-O., de Haan, B. (in preparation). Anatomical substrates of visual extinction: A multivariate lesion analysis study in acute stroke

Christoph Sperber: Conceptualisation, Formal analysis, Methodology, Investigation, Writing - original draft. Daniel Wiesen: Formal analysis, Methodology, Investigation, Writing - review & editing. Hans-Otto Karnath: Resources, Writing - review & editing. Bianca de Haan: Conceptualisation, Formal analysis, Methodology, Investigation, Supervision, Writing - original draft.

9 Appended papers/manuscripts

Using machine learning-based lesion behavior mapping to identify anatomical networks of cognitive dysfunction: Spatial neglect and attention

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Using machine learning-based lesion behavior mapping to identify anatomical networks of cognitive dysfunction: Spatial neglect and attention

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ABSTRACT

Previous lesion behavior studies primarily used univariate lesion behavior mapping techniques to map the anatomical basis of spatial neglect after right brain damage. These studies led to inconsistent results and lively controversies. Given these inconsistencies, the idea of a wide-spread network that might underlie spatial orientation and neglect has been pushed forward. In such case, univariate lesion behavior mapping methods might have been inherently limited in detecting the presumed network due to limited statistical power. By comparing various univariate analyses with multivariate lesion-mapping based on support vector regression, we aimed to validate the network hypothesis directly in a large sample of 203 newly recruited right brain damaged patients. If the exact same correction factors and parameter combinations (FDR correction and dTLVC for lesion size control) were used, both univariate as well as multivariate approaches uncovered the same complex network pattern underlying spatial neglect. At the cortical level, lesion location dominantly affected the temporal cortex and its borders into inferior parietal and occipital cortices. Beyond, frontal and subcortical gray matter regions as well as white matter tracts connecting these regions were affected. Our findings underline the importance of a right network in spatial exploration and attention and specifically in the emergence of the core symptoms of spatial neglect.

1. Introduction

Spatial attention and orientation is a cognitive function dominantly represented in the human right hemisphere (Corbetta et al., 2008, 2005). In correspondence, spatial neglect is one of the most common syndromes after brain injury of predominantly this hemisphere (Stone et al., 1993; Becker and Karnath, 2007; Ten Brink et al., 2017). Patients spontaneously and sustainably deviate towards the ipsilesional side, neglecting contralesionally located information or stimuli (Heilman et al., 1983; Karnath and Rorden, 2012). The anatomical basis of this core deficit of spatial neglect has been extensively investigated using mass-univariate lesion behavior mapping methods (VLBM), such as VLSM (Bates et al., 2003) or NPM (Rorden et al., 2007). Heterogeneous findings were observed, causing lively controversies (for review Karnath and Rorden, 2012). In the right hemisphere, spatial neglect has been reported to be associated with parietal lesions to regions in the inferior parietal lobule and temporo-parietal junction (Chechlacz et al., 2010; Karnath et al., 2011; Rousseaux et al., 2015), the superior and middle temporal cortex as well as the insula (Karnath et al., 2004, 2011; Committeri et al., 2007; Sarri et al., 2009; Chechlacz et al., 2010; Saj et al., 2012; Rousseaux et al., 2015) and the ventrolateral prefrontal cortex (Committeri et al., 2007; Thiebaut De Schotten et al., 2014). These cortical areas were also found to be involved in the human left hemisphere when patients show spatial neglect after a left hemisphere stroke (Suchan and Karnath, 2011). Furthermore, disrupted structural connectivity has been related to spatial neglect, including damage of the superior longitudinal fasciculus and arcuate fasciculus, the inferior occipito-frontal fasciculus, extreme capsule and the superior occipito-frontal fasciculus, as well as the middle longitudinal fasciculus (Thiebaut de Schotten et al., 2005; He et al., 2007; Urbanski et al., 2008, 2011; Karnath, 2009; Shinoura et al., 2009; Ciaraffa et al., 2013; Thiebaut De Schotten et al., 2014; Umarova et al., 2014; Vaessen et al., 2016; Carter et al., 2017; de Haan and Karnath, 2017).

Abbreviations: VLBM, Voxel-based lesion behavior mapping; MLBM, Multivariate lesion behavior mapping; SVR, Support vector regression; SVR-LSM, Support vector regression based lesion-symptom mapping; FDR, false discovery rate; FWE, Family Wise Error; dTLVC, Direct Total Lesion Volume Control.

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Hence, building on the seminal work by Watson et al. (1974) and Mesulam (1981), it has been concluded in review articles (Catani, 2006; Bartolomeo et al., 2007; Karnath, 2009; Karnath and Rorden, 2012; Lunven and Bartolomeo, 2017) and meta-analyses (Chechlacz et al., 2012; Molenberghs et al., 2012) that an anatomical network (Karnath, 2009; Karnath and Rorden, 2012) might represent the basis of spatial neglect.

Part of the heterogeneity in the anatomical correlates of spatial neglect may be determined by the fact that the different studies were varying largely in the application of different analysis procedures and methodological choices, including e.g. statistical tests, statistical thresholding, corrections for multiple comparisons, or procedures for lesion volume control. In fact, statistical lesion behavior mapping approaches provide many degrees of freedom and pitfalls to a researcher (for review, see Sperber and Karnath, 2018). Beyond, the statistical analysis techniques themselves each come along with specific strength and weaknesses. For example, traditional mass-univariate lesion behavior mapping methods can be ill-suited in situations, where lesions of multiple brain areas contribute to a pathological behavior. Due to the so-called 'partial injury problem' (Rorden et al., 2009; Sperber et al., 2019), statistical power of VLBM in anatomical networks might be reduced, and false negative findings might conceal the full network. This issue has been confirmed by several simulation studies (Mah et al., 2014; Zhang et al., 2014; Pustina et al., 2018). Furthermore, the huge number of independent tests in VLBM as well as in some of the multivariate lesion behavior mapping (MLBM) implementations requires control for multiple comparisons, which can further reduce statistical power. This might have contributed to the heterogeneous pattern of previous results in spatial neglect, with different studies identifying some nodes while missing others. Additional facts which can explain heterogeneous anatomical findings might be based on the specific sample characteristics in previous investigations (Gajardo-Vidal et al., 2018). The authors showed that specific sub-sets of patients can drive significant results. This might be especially true in smaller studies with lower power (Lorca-Puls et al., 2018).

Unlike VLBM's mass-univariate testing approach, machine learning based lesion analysis offers a multivariate approach to lesion analysis. Multivariate lesion behavior mapping (MLBM) appears to be particularly suitable to identify neural correlates of behavior organized in networks (Smith et al., 2013; Mah et al., 2014; Zhang et al., 2014; Yourganov et al., 2015; Zavaglia and Hilgetag, 2016; Pustina et al., 2018; for review Karnath et al., 2018). Two recent studies investigated the neural correlates of spatial neglect with MLBM, one using support vector machines in a sample of 140 right hemisphere stroke patients (Smith et al., 2013), the other a game theoretical approach in a small sample of only 25 (and even less for subtests) right hemisphere patients (Toba et al., 2017). Both studies had limitations. The two approaches were constrained to the investigation of only a few brain regions at once, in other words, these approaches did not provide a voxel-by-voxel analysis of the lesion pattern throughout the brain. Moreover, regions in such region-based approaches can differ both from the relevant functional parcellation of the brain and the typical anatomy of stroke lesions and thus might have failed to capture relevant brain regions. In contrast, Support Vector Regression based Multivariate Lesion-Symptom Mapping (SVR-LSM) utilizes voxel-wise whole brain information independently of an a priori region of interest selection (Zhang et al., 2014). Different groups have recently validated and tested this approach (Zhang et al., 2014; DeMarco and Turkeltaub, 2018; Sperber et al., 2019).

Further, we assume that part of the apparent diversity in previous anatomical results reflects small sample sizes used in part of the previous studies. Moreover, many prior studies have treated neglect as a categorical deficit, whereas there is clear evidence that the symptom severity varies between individuals (Rorden and Karnath, 2010). Likewise, some prior studies have measured attentional deficits that dissociate from each other (Karnath and Rorden, 2012). If these sources of variability in impairment correlate with the location and extent of injury, studies that treat neglect as merely present or absent may suffer further reduced power. Therefore, the aim of the present study is to use anatomical data from a large sample of 203 newly recruited right hemisphere damaged patients in order to apply and compare several univariate VLBM techniques as well as the multivariate SVR-LSM method (Zhang et al., 2014) to identify the anatomical representation underlying spatial neglect. For the comparison of methods, we focus especially on those VLBM techniques that correspond to the majority of the current univariate lesion-mapping studies (for review, see de Haan and Karnath, 2018), addressing a cross-section of statistical thresholding methods and procedures for lesion volume control.

Moreover, in order to reduce the possible influence of different symptoms of and clinical tests for spatial neglect, we here focus on only the egocentric core component of spatial neglect (see Karnath and Rorden, 2012), using a continuous measure to capture symptom severity. This core component is represented by a spontaneous and sustained deviation of eyes and head towards the ipsilesional side (Fruhmann-Berger and Karnath, 2005; Fruhmann-Berger et al., 2006; Becker and Karnath, 2010), combined with neglect of contralesionally located information or stimuli. This spatial bias can be reliably measured amongst others by traditional cancellation tasks (Rorden and Karnath, 2010) as well as a modified line bisection task (McIntosh et al., 2017). As noted, several spatial and non-spatial attentional symptoms that have been associated with neglect patients (e.g. Binder et al., 1992; Husain et al., 1997; Barton and Black, 1998; Ferber and Karnath, 2001; Azouvi, 2002; Husain and Rorden, 2003; Verdon et al., 2010; Sperber et al., 2016; McIntosh et al., 2017), though many of these symptoms can dissociate both anatomically and behaviorally. Our goal was to have a robust and pure measure for the core spatial bias, uncontaminated by these other symptoms.

2. Materials and methods

2.1. Subjects

Neurological patients consecutively admitted to the Center of Neurology at Tuebingen University were screened for a first ever right-hemisphere stroke. Patients with a left-sided stroke, patients with diffuse or bilateral brain lesions, patients with tumors, as well as patients in whom MRI or CT scans revealed no obvious lesions were not included. In total 203 patients were recruited in the acute phase after stroke (3.2 and 4.2 days post-stroke on average; cf. Table 1). None of these patients were included in any of our previous studies addressing the anatomy of spatial neglect (Karnath et al., 2001, 2004; 2011; Smith et al., 2013). Therefore, they represent an independent, new sample. Table 1 gives the demographic and clinical data. All subjects provided written informed consent and the study was conducted in accordance with the ethical guidelines from the revised Declaration of Helsinki and in accordance with relevant guidelines and regulations.

2.2. Behavioral examination

The interval between stroke-onset and neuropsychological examination was maximally 25 days (mean = 4.37 days, SD = 4.04). The following neuropsychological tests were performed: Letter Cancellation Task (Weintraub and Mesulam, 1985) and Bells Test (Gauthier, Louise Dehaut, Francois Joanette, 1989). These two tests were presented on a horizontally oriented 21 × 29.7 cm sheet of paper which was fixed at the center of the patient's sagittal midline. In the Letter Cancellation task, 60 target letters 'A' are distributed among other distractor letters. The Bells test requires identifying 35 bell icons distributed all over the sheet between other symbols. In these two cancellation tasks, patients were asked to cancel all of the targets, 'A' letters or bells respectively. The maximum duration of each test was not fixed in advance but depended on the patient being satisfied with his performance and confirming this twice. For the Letter and Bells Cancellation tasks, we calculated the Center of Cancellation (CoC) using the procedure by Rorden and Karnath (2010).

The CoC is a sensitive measure capturing both the number of omissions, as well their location. For the lesion behavior mapping, we calculated the mean CoC from the two cancellation tasks for each patient and used this score for our analyses. Visual field defects were examined by the common neurological confrontation technique.

2.3. Imaging

Structural imaging was acquired either by MRI (n = 106) or CT (n = 97), performed on average 3.5 days (SD = 4.6) after stroke-onset. If both imaging modalities were available, MR scans were preferred. In participants where MR scans were available, we used diffusion-weighted imaging (DWI) if the images were acquired within 48 h after stroke onset or T2-weighted fluid attenuated inversion recovery (FLAIR) images for later scans. Lesion boundaries were manually marked on the transversal slices of the individual MR or CT scans using the free MRIcron software (www.mccauslandcenter.sc.edu/mricro/mricron).

Normalization of CT or MR scans to MNI space with 1x1x1 mm resolution was performed by using the Clinical Toolbox (Rorden et al., 2012) under SPM8 (www.fil.ion.ucl.ac.uk/spm), and by registering lesions to its age-specific templates oriented in MNI space for both CT and MR scans (Rorden et al., 2012). If available, the MR scans were co-registered with a high resolution T1-weighted structural scan in the normalization process. Delineation of lesion borders and quality of normalization were verified by consensus of always two experienced investigators (one of them H.-O.K.). An overlap of all normalized lesions is shown in Fig. 1. The average lesion size in the sample was 45.52 cm^3 (SD = 52.67 cm^3). In the supplemental material we show overlap plots of normalized lesions separated for each imaging modality (Fig. S1) as well as a histogram of the lesion size distribution (Fig. S2 B). Moreover, we provide a figure showing the regional bias caused by lesion volume (Fig. S3).

2.4. Multivariate lesion behavior mapping

2.4.1. Support vector regression

For our analysis, we implemented a multivariate lesion-symptom mapping method based on support vector regression (SVR) (Drucker et al., 1996; Vapnik, 1995). Lesion mapping based on support vector regression employs supervised machine learning algorithms to develop a model based on training input data which best describes the continuous relationship between behavioral scores and lesion location. Hence, it can be seen as an extension of Support Vector Machines (SVM) (Cortes and Vapnik, 1995) used for classifying data sets into different categories. Support vector regression based lesion-symptom mapping (SVR-LSM) has already been implemented and validated in a synthetic dataset, in a real dataset composed of aphasic patients (Zhang et al., 2014), as well as several recent publications (Xing et al., 2015; Fama et al., 2017; Griffis et al., 2017a,b; Lacey et al., 2017; Skipper-Kallal et al., 2017; Chen et al., 2018; DeMarco and Turkeltaub, 2018; Zhao et al., 2018; Sperber et al., 2019).

Table 1
Demographic and clinical data of the 203 patients included.
For this table we determined whether a CoC (= Center of Cancellation; see Rorden and Karnath, 2010) score was in the pathological range; cut-offs were set at >0.081 for the Bells Cancellation Task and >0.083 for the Letter Cancellation test (cf. Rorden and Karnath, 2010). In order to assign the diagnosis of spatial neglect, patients had to present a pathological test score in at least one of the two cancellation tests. Using this criterion, 81 (40%) were classified as exhibiting spatial neglect while 122 (60%) did not exhibit neglect. Data are represented as mean (SD). Note that in the statistical tests we treated neglect severity as a continuous measure. The table reveals that using cut-off thresholds, there is little variability in patients without pathological bias (ceiling performance), while symptom severity varies across patients with pathological deficits.

	Neglect	No neglect
Age (years)	64.7 (12.4)	60.2 (13.7)
Sex (M/F)	48/33	71/51
Etiology (Ischemia/Hemorrhage)	69/12	104/18
Lesion size (cm^3)	70.0 (64.4)	29.3 (35.0)
Time since lesion (days)	4.2 (4.3)	3.2 (4.5)
Letter Cancellation (CoC)	0.36 (0.32)	0.01 (0.02)
Bells Cancellation (CoC)	0.39 (0.29)	0.01 (0.03)
Visual Field Defects (% present)	27	14
Imaging (CT/MRI)	44/37	53/69

Data Analysis. The analysis was performed with MATLAB 2016a and libSVM Vers. 3.21 (Chang and Lin, 2013). We used a publicly available collection of scripts (https://github.com/yongsheng-zhang/SVR-LSM) employed in the study by Zhang et al. (2014) and adopted algorithms for control for lesion size and for the derivation of a topography from SVR β-parameters. For the detailed methodological procedure and theoretical background of SVR-LSM in general, see Zhang et al. (2014). Only voxels where at least 10 patients had a lesion were included in the analysis and constituted the voxel mask for statistical testing. Exclusion of voxels with infrequent lesion affection was performed to restrict the analysis to voxels with reasonable statistical power and thus to reduce the potential that the results are biased by brain regions that are only rarely affected (Karnath et al., 2018). The employed analysis is therefore no strict whole-brain analysis, but – contrary to region-of-interest analyses – it allows an investigation of all brain areas that contain a certain degree of information. First, the lesion status of each participant was regrouped into a column vector. To control for lesion size, each vector was then normalized to have a unit norm, a procedure also known as direct total lesion volume control (dTLVC) (Zhang et al., 2014). Lesion volume control is an important preprocessing step as the severity of a symptom is generally related to the lesion size, as shown for our data ($r = 0.54$; $p < 0.001$) in Fig. S2 A in the supplemental material. To ensure, that this latter correlation is not solely driven by a few patients having very large lesions >150 cm^3, we further report the correlation for the subset of patients having lesions <150 cm^3 (N = 195). Although the strength of the association decreases to some degree, lesion size stays significantly related to the severity of the spatial neglect behavior ($r = 0.43$; $p < 0.001$). To estimate the SVR hyperplane and project our initial data into a higher dimensional space, we implemented an epsilon-SVR model and used a non-linear radial basis function (RBF) Kernel. In order to improve the performance of the learning algorithms and to choose a model best describing our data, a preselection of the model hyper-parameters cost (C) and gamma (γ) needs to be done. Following general recommendations in the libSVM toolbox manual (Chang and Lin, 2013), we added an optimization procedure using grid search. The range of investigated parameters was chosen as in the study by Zhang et al. (2014): C = 1, 10, 20, 30, 40, 50, 60, 70, 80, and γ = 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30. Using a five-fold cross-validation scheme, we evaluated both prediction accuracy and reproducibility of each parameter combination (see Zhang et al., 2014). During this procedure, the whole dataset is separated into 4/5 training data, which is used to generate the multivariate model. Then this model is tested on the unknown leftover 1/5 of the data to prevent overfitting and to get a good estimate of the performance of the model to unknown data. To save computational power, we reduced the number of iterations from 40 to 5 compared to the initial analysis in Zhang et al. (2014) and evaluated mean prediction accuracy and reproducibility scores, based on these 5 iterations for each parameter set. We define mean prediction accuracy, as in Zhang et al. (2014), to be the mean correlation coefficient between predicted scores and out of sample testing scores of 5 times 5-fold cross-validations. Note that for each of the 5 iterations, new random subsets of training and testing scores were drawn from the whole dataset. After SVR model construction, β-parameters are remapped onto a three-dimensional brain topography allowing us to derive the reproducibility score by calculation of the mean correlation coefficient between any two SVR-LSM β-parameter maps from the drawn subsets. Finally, using the best combination of C and γ for model construction, the remapped β-parameters are tested by using a permutation approach,

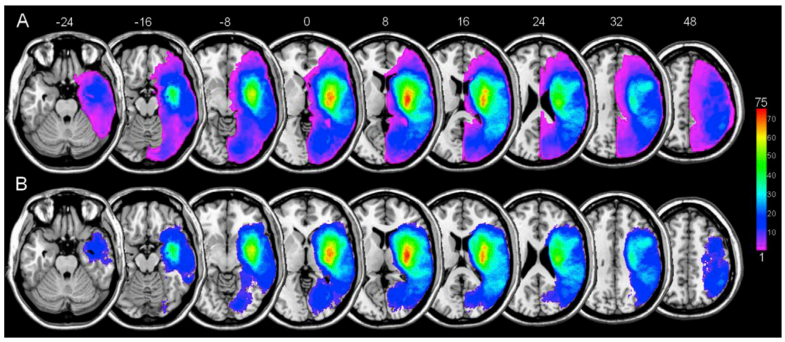

Fig. 1. Topography of brain lesions. A: Simple lesion overlap topography of all 203 patients. **B:** Lesion overlap topography showing only voxels within the voxel mask for statistical testing with at least 10 patients having a lesion. The colorbar indicates the number of overlapping lesions (the peak of N = 75 represents 37% of the total sample). Numbers above the slices indicate z-coordinates in MNI space.

comparing the SVR β-parameters voxel-wise with new β-parameters drawn for each permutation through randomization of behavioral scores. Results are reported with correction for multiple comparisons that survived a False Discovery Rate (Benjamini and Yekutieli, 2001) (FDR) correction at $q = 0.05$, determined by 10000 permutations. As statistical testing is performed on a voxel-by-voxel basis, a form of multiple comparison correction is required to prevent an increase of false alarms (Sperber et al., 2019).

2.5. Univariate voxel-based lesion behavior mapping

To compare the SVR-LSM technique with traditional analyses, we also performed mass-univariate VLBM analyses on the same data set. As for MLBM, only voxels where at least 10 patients had a lesion were included in the analysis and constituted the voxel mask for statistical testing. The variants of lesion volume correction and correction for multiple comparisons differ between univariate studies. Nevertheless, the exact choice might have an impact on the topographical outcome of the univariate results, as shown recently by Pustina et al. (2018). Therefore, we decided to show results using different parameter configurations, providing a small cross section of what is currently employed in the field. Hence, for the univariate analyses, there were in total 4 configurations: A) without correction for lesion size including family-wise error correction (FWE) for multiple comparisons based on 10000 permutations at $p < 0.05$; B) with correction for lesion size – by regressing lesion size out of behavior – including FWE correction for multiple comparisons based on 10000 permutations at $p < 0.05$; C) without correction for lesion size including False Discovery Rate (FDR) correction for multiple comparisons at $q = 0.05$; D) with correction for lesion size – by regressing lesion size out of behavior – including FDR correction for multiple comparisons at $q = 0.05$. Finally, to increase comparability to our multivariate findings, we additionally performed one analysis with similar parameter configurations, using minimum lesion affection of 10, FDR correction for multiple comparisons at $q = 0.05$, as well as dTLVC as lesion volume control procedure.

All univariate analyses were carried out using the NiiStat tool (https://github.com/neurolabusc/NiiStat) and were based on the general linear model (identical to a Student's pooled-variance *t*-test). To get a further direct quantitative comparison between multivariate and univariate mapping models, we compared the predictive performance of both techniques using the same parameter configurations in terms of lesion volume control and minimum lesion affection. Hence, for the univariate lesion behavior mapping, we implemented a 5 times 5-fold procedure on each single voxel and derived the predictive performance in terms of R^2, using the same parameter configurations as for our main multivariate analysis. Therefore, minimum lesion affection was set to $N = 10$ and the dTLVC procedure to control for lesion volume was used. During this procedure, the whole dataset was separated into 4/5 training data, which is used to generate a univariate model for each single voxel. Subsequently, this model was tested on the unknown leftover 1/5 of the data to prevent overfitting and to get a good estimate of the performance of the model to unknown data. We then evaluated mean prediction performance in terms of R^2 based on these 5 iterations for each voxel. We defined mean prediction performance to be the mean R^2 value between predicted scores and out of sample testing scores of 5 times 5-fold cross-validations. Note that for each of the 5 iterations new random subsets of training and testing scores were drawn from the whole dataset. Finally, we evaluated if the predictive performance of the multivariate model is superior to each of the models of each single voxel when univariate mapping is used.

2.6. Supplementary analysis

While the need of lesion volume correction is widely accepted, the exact technique to be used is still under discussion. Zhang et al. (2014) validated the dTLVC method for real and synthetic lesion data and argued that a regression based correction might be excessively conservative. On the other hand, DeMarco and Turkeltaub (2018) put forward that the dTLVC method might be too liberal and advocated for using regression based correction. To address both positions and concerns, we implemented a supplemental analysis using the same parameters as for our main SVR-LSM analysis, except for now regressing lesion size out of both behavioral and lesion scores instead of the dTLVC procedure. Scripts for this supplemental analysis have been adopted from a recently published toolbox and are available online (github.com/atdemarco/svrlsmgui; DeMarco and Turkeltaub, 2018).

2.7. Atlas overlap

Labeling of all the resulting voxel-wise statistical maps with respect to grey matter brain regions was done by overlaying the maps on the Automatic Anatomical Labelling atlas (AAL; Tzourio-Mazoyer et al., 2002) distributed with MRIcron. The localization of white matter fiber tracts damaged by the lesion was based on two different fiber tract atlases: the Juelich probabilistic cytoarchitectonic atlas (Bürgel et al., 2006) as well as the tractography-based probabilistic fiber atlas (Thiebaut de Schotten et al., 2011). We decided to interpret the data according to these two WM atlases simultaneously due to the marked variance between DTI- and histology-based white matter atlases (de Haan and Karnath, 2017). The WM probabilistic maps were thresholded at $p \geq 0.3$ before being overlaid on the statistical topography.

3. Results

3.1. Parameter optimization

Testing different sets of C and γ combinations, we got a similar pattern of that what has already been reported in previous investigations (Rasmussen et al., 2012; Zhang et al., 2014). Thus, the C and γ variables provide a trade-off between prediction accuracy and reproducibility (Fig. 2 A and B). Without having any reference about a certain standard in choosing the right parameter combination, we decided to perform the final analysis with a C of 30 and γ of 4, as these values provided, compared to the other combinations, a decent prediction accuracy (0.43) while keeping the reproducibility index (0.91) as high as possible. With this combination, the model achieves an average cross-validation R^2 of 0.19, averaged over runs and folds from the repeated 5-fold cross-validation scheme. Note that these values have been drawn from the 5 times 5-fold cross-validation optimization routine and hence reflect the model performance when 4/5 of the dataset were used for model creation and 1/5 for model testing. It is worth noting that the R^2 reflects prediction after one has accounted for lesion volume (see section 2.6 above). Note that lesion volume is virtually always a strong predictor of behavior: large lesions are likely to compromise sufficient portions of distribute networks and large hubs to elicit symptoms, and larger lesions are probabilistically more likely to hit small modules than smaller injuries. Therefore, the reported R^2 are with respect to the residual variability after the strong factor is accounted for. This has clear implications for clinical prognosis, where both lesion volume and location can be leveraged.

3.2. Multivariate lesion behavior relationships

Resulting topographies of the SVR-LSM analysis using continuous CoC scores revealed a perisylvian network including parietal, frontal and temporal grey matter regions as well as clusters in WM fibers (Fig. 3). An exact overview of the grey and white matter structures significantly involved and showing at least 100 mm^3 overlapping voxels with the respective atlas structures is given in Table 2. Large clusters incorporated middle and superior temporal gyri as well as the inferior parietal lobule, including angular and supramarginal gyri. Smaller clusters affected inferior and middle frontal gyri, as well as the pre- and postcentral gyri. Moreover, significant lesion patterns included the insula and subcortical structures such as the pallidum, putamen and caudate nucleus. The overlap with both WM atlases consistently showed significant clusters affecting the uncinate fasciculus and the inferior occipito-frontal fasciculus. In addition, only the WM atlas by Thiebaut de Schotten et al. (2011) implicated the inferior longitudinal, as well as the superior longitudinal/arcuate fasciculus and the internal capsule, while only the Juelich WM atlas identified the superior occipito-frontal fasciculus. In addition, Fig. 3D the thresholded β–map of the SVR-LSM analysis is plotted, showing the association between individual voxel-wise β-weight to the behavioral score (see Sperber et al., 2019).

3.3. Univariate voxel-based lesion behavior relationships

The VLBM analysis most similar to the MLBM procedure, using FDR correction and dTLVC for lesion size control, revealed a lesion pattern which concurs largely with that of the MLBM results (Fig. 4 and Table 3A).

In contrast, the VLBM analysis including family-wise error correction (FWE) for multiple comparisons without correction for lesion size (Fig. 5A) revealed mainly involvement of inferior and middle frontal as well as middle and superior temporal cortical grey matter areas. Moreover, subcortical affection of the putamen, caudate nucleus, and pallidum was seen; no significant effects were detected in parietal cortex. A detailed overview of grey and white matter structures significantly involved and with at least 100 mm^3 overlap with the respective atlases is given in Table 3B. The comparison with white matter atlases reveals involvement of the superior occipito-frontal fasciculus for the Juelich WM atlas as well as the arcuate and uncinate fasciculi for the WM atlas by Thiebaut de Schotten et al. (2011). Moreover, the latter delineated affection of the inferior occipito-frontal and longitudinal fasciculi, as well as the internal capsule.

The VLBM analysis including family-wise error correction (FWE) and a correction for lesion size (Fig. 5B) revealed only a small cluster within frontal white matter. The univariate analysis using FDR-thresholding without correction for lesion size is showing a wide spreading map with 56% of the tested voxels becoming significant, spanning over frontal, temporal, parietal and occipital as well as subcortical areas and clusters in white matter fibres (Fig. 5C). A detailed overview of grey and white matter structures significantly involved and with at least 100 mm^3 overlap with the respective atlases is given in Table 3C. On the other side, employing lesion volume correction, the analysis with FDR-thresholding showed a rather conservative pattern – similar to FWE-thresholding with correction for lesion size – of two small clusters in the frontal white matter with no corresponding atlas label (Fig. 5D).

3.4. Quantitative comparison between univariate and multivariate lesion-behavior mapping

The comparison of the predictive performance between univariate and multivariate procedures showed that the predictive performance in terms of R^2 (cross-validation R^2, averaged over runs and folds from the repeated 5-fold cross-validation scheme) of each single voxel in univariate lesion behavior mapping yielded a maximum R^2 of 0.21. On the first

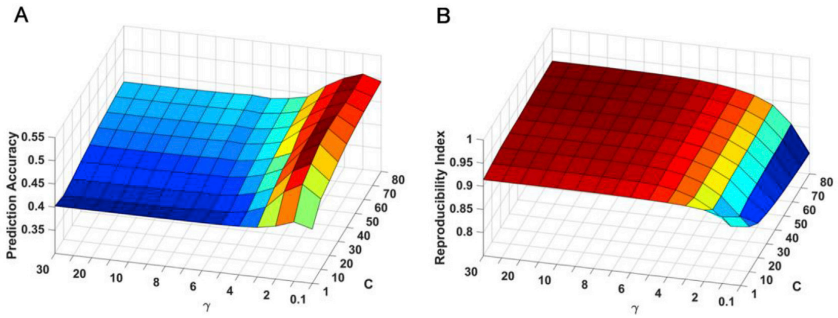

Fig. 2. Estimation of best hyper-parameters C and γ. SVR-LSM parameter estimation results. Prediction Accuracy (**A**) and Reproducibility Index (**B**) (see Rasmussen et al., 2012; Zhang et al., 2014) are plotted for the different sets of C and **γ** parameters to find the optimal combination.

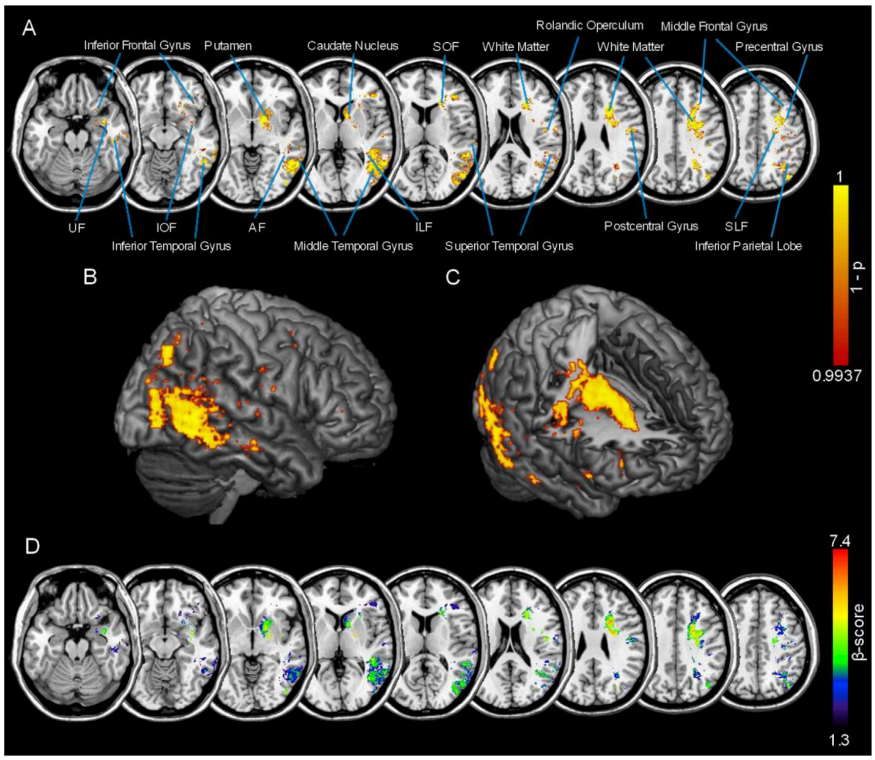

Fig. 3. Results of the multivariate lesion behavior mapping. Support vector regression based multivariate lesion-symptom mapping results using data of 203 patients. Lesion volume correction was performed by applying dTLVC. A: Permutation-thresholded statistical map of SVR-LSM on CoC scores (FDR-corrected at $q = 0.05$, corresponding to a threshold of $p < 0.0063$), illustrating the anatomical regions significantly associated with the core deficit of spatial neglect. Significant clusters were interpreted according to the AAL atlas (Tzourio-Mazoyer et al., 2002) for grey matter regions and to the Juelich probabilistic cytoarchitectonic fiber tract atlas (Bürgel et al., 2006) as well as the tractography-based probabilistic fiber atlas by Thiebaut de Schotten et al. (2011) for white matter structures. B and C: three-dimensional renderings of the same map using the 3D-interpolation algorithm provided by MRIcron (http://people.cas.sc.edu/rorden/mricron/index.html; 8 mm search depth) with sagittal view for B and inside view for C. Results of A, B and C are shown as 1-p. D: Thresholded β-parameter map showing only significant areas according to A. Abbreviations: SLF – superior longitudinal fasciculus; AF – arcuate fasciculus; ILF – inferior longitudinal fasciculus; IOF – inferior occipitofrontal fasciculus; SOF – superior occipitofrontal fasciculus; UF – Uncinate fasciculus.

sight, this seems superior to the R^2 of 0.19 – both R^2 values after correcting for lesion volume – found for multivariate mapping. Nevertheless, for univariate lesion behavior mapping only 12 voxels exceeded the R^2 of 0.19. The location of these 12 voxels corresponded spatially to the spot in frontal white matter that we obtained in all of the univariate lesion behavior mapping topographies with highest z-scores (see Fig. 5); it might reflect an area with largest power across all of our univariate analyses. On the other side, the prediction performance of all the other voxels throughout the tested area in univariate modelling was inferior to the multivariate model (all $R^2 < 0.19$). To make sure that the overall multivariate model is indeed better and the predictive performance not only driven by the same 12 voxels, which show the most predictive individual contribution in VLBM, we repeated the cross-validation scheme for SVR-LSM with exclusion of these 12 voxels. By excluding these voxels, this further evaluation results in a predictive performance of $R^2 = 0.187$ and confirms that the multivariate model is not driven by only a few single voxels. A figure showing the frequency distribution of all mass-univariate R^2 values with the location of the multivariate R^2 values including as well as excluding the 12 maximum voxels of the univariate analysis is shown in the supplement (Fig. S4).

3.5. Supplementary analysis

In a recent investigation, it has been advocated for the use of a new technique for correction for lesion size (e.g. regression of lesion volume out of both, behavior and lesion). Therefore, we implemented a supplemental analysis using the same parameters as for our main SVR-LSM analysis, except for now regressing lesion size out of both behavioral and lesion scores instead of the dTLVC procedure. The optimization procedure delineated a C of 1 and γ of 0.1 as optimal parameters revealing a prediction accuracy of −0.02 and a reproducibility index of 0.88. With this combination, the model achieves an $R^2 < 0.001$. Results for the supplemental analysis revealed a much more conservative pattern as compared to the SVR-LSM analysis with dTLVC correction. If we regress lesion size out of both behavioral and lesion scores, the resulting topographies centered on several smaller nodes (see Supplementary Material; Fig. S5). One cluster of lesion symptom associations was found within the right basal ganglia (putamen, pallidum, head of caudate nucleus). Moreover, an anterior cluster was revealed within the white matter adjacent to inferior and middle frontal gyri. A further small node was found at the right middle/inferior temporal cortex.

Table 2
Detailed overview of all significant grey and white matter clusters – MLBM. Overlap of MLBM analysis with grey and white matter atlases (FDR-corrected at $q = 0.05$, corresponding to a threshold of $p < 0.0063$). For grey matter structures, reports are generated using the Automatic Anatomical Labeling atlas (AAL; Tzourio-Mazoyer et al., 2002). For white matter structures, reports are generated using the Juelich probabilistic cytoarchitectonic atlas (Bürgel et al., 2006) and the tractography-based probabilistic fiber atlas by Thiebaut de Schotten et al. (2011) defined at a probability of $p \geq 0.3$. Only structures with at least 100 mm^3 of overlapping voxels were reported in the table.

GM structure (AAL)	Number of voxels (mm^3)	β (Mean/SD)	β (Peak)
Middle temporal gyrus	8441	3.13/0.60	5.66
Inf. temporal gyrus	3078	2.59/0.57	4.40
Middle occipital gyrus	1677	3.37/0.61	5.73
Angular gyrus	1398	3.14/0.58	4.45
Sup. temporal gyrus	968	3.01/0.54	5.10
Pallidum	848	4.35/1.09	7.03
Middle frontal gyrus	739	2.62/0.53	4.73
Caudatum	719	3.24/0.63	5.72
Inf. frontal gyrus/triangular	706	2.23/0.23	3.99
Postcentral gyrus	570	2.92/0.35	4.17
Putamen	481	3.71/0.74	6.54
Rolandic operculum	422	3.74/0.53	5.22
Precentral gyrus	346	3.07/0.66	5.38
Inf. frontal gyrus/orbital	314	3.80/0.58	4.41
Amygdala	279	2.96/0.49	5.25
Supramarginal gyrus	228	2.88/0.35	3.73
Inf. occipital gyrus	214	3.45/0.95	5.23
Inf. parietal gyrus	166	2.81/0.24	3.68
Insula	119	3.00/0.93	5.99
Hippocampus	115	3.07/0.64	4.87
Sup. temporal pole	113	2.54/0.54	3.98
WM structure (Juelich)	**Number of voxels (mm^3)**	**β Mean/SD)**	**β (Peak)**
Callosal body	2703	4.10/1.09	7.31
Optic radiation	1393	3.07/0.67	5.48
Corticospinal tract	832	3.52/0.98	6.14
Sup. occipito-frontal fasciculus	262	4.26/0.91	6.84
Inf. occipito-frontal fasciculus	168	4.56/0.56	6.30
Uncinate fasciculus	134	4.36/0.68	6.30
WM structure (Thiebaut de Schotten)	**Number of voxels (mm^3)**	**β (Mean/SD)**	**β (Peak)**
Corpus callosum	3245	4.05/1.01	7.39
Internal capsule	2846	4.28/1.05	7.23
Inf. longitudinal fasciculus	2545	3.10/0.67	5.48
Arcuate fasciculus	2315	3.15/0.61	5.42
Posterior segment (Arcuate)	2036	3.07/0.58	4.88
Corticospinal tract	1845	4.19/1.07	7.23
Uncinate fasciculus	1249	3.26/0.82	6.30
Cingulum	1200	3.39/0.61	5.37
Anterior commissure	1177	3.21/0.85	5.88
Inf. occipito-frontal fasciculus	798	3.49/0.81	5.98
Optic radiations	306	3.37/0.66	5.42
Anterior segment (Arcuate)	282	3.71/0.57	5.42
Sup. longitudinal fasciculus	144	3.04/0.33	4.87

4. Discussion

The present study examined the lesion behavior relationship of spatial neglect in a newly recruited sample of right brain damaged patients. If the exact same methodological parameter configuration in terms of lesion volume correction and statistical thresholding (FDR correction and dTLVC for lesion size control) were used, both univariate as well as multivariate approaches revealed – in a single analysis – the same, complex network pattern underlying spatial neglect. At the cortical level, lesion location dominantly affected superior and middle temporal cortex and its borders into inferior parietal and occipital cortex. Beyond, parts of the insula and the inferior and middle frontal gyri were affected. Subcortically, we observed affection of parts of the pallidum, putamen and caudate nucleus as well as white matter fiber tracts, such as the superior and inferior longitudinal fasciculi, the superior and inferior occipito-frontal fasciculi, and the uncinate fasciculus. We further compared VLBM and MLBM methods by the predictive performance of both, the overall multivariate lesion behavior mapping model to the predictive performance of each individual voxel in univariate lesion behavior mapping after using dTLVC as lesion volume control procedure. This latter analysis showed that only few voxels were able to perform better than the combination of all voxels together in the multivariate model and that the predictive performance of the multivariate mapping technique was generally superior.

Despite the large sample size, the univariate analyses with lesion volume control by nuisance regression only detected one cluster in frontal white matter after FWE correction. A similar pattern was shown after using FDR correction with two small clusters in frontal white matter. Following results of these analysis, the univariate VLBM had enough power to generate a statistical map which was qualitatively comparable to the multivariate SVR-LSM map only when keeping residual signal of lesion size in the model. In the VLBM analysis including FWE correction, the univariate processing detected most of the regions that were also detected by the SVR-LSM analysis, with the exception of the inferior parietal lobule. The major difference was that VLBM detected massively less signal, resulting in only few actually interpretable clusters. In contrast, the VLBM analysis including FDR thresholding showed a more liberal pattern with a large number of detections. Some of these detections might not be directly linked to spatial neglect, but rather reflect areas with high lesion volume coverage, limiting the interpretation on the spatial extend of neglect behavior. Hence, it should be noted that the results of the latter two analyses were coupled to the omission of lesion volume control. However, since the severity of a behavioral symptom is often strongly correlated with total lesion volume and larger lesions are more likely to affect critical anatomical areas (Karnath et al., 2004), a form of correction is desired to detect the neural correlate specific to the behavioral symptom of interest. The comparison between the FDR thresholded statistical map without lesion volume control (Fig. 5C) and the average lesion volume plot (Fig. S3) revealed that the statistical topography might be biased towards areas with relatively large average lesion volumes. This impression could be quantitatively confirmed by a significant correlation between the unthresholded univariate statistical map – z-scores – without lesion volume correction and the lesion overlap plot ($r = 0.57$; $p < 0.001$). Please note that the correlation was also present for the unthresholded multivariate β-score map without lesion volume correction ($r = 0.31$; $p < 0.001$).

As expected, the regression technique suggested by DeMarco and Turkeltaub (2018) to control for lesion size turned out to be much more conservative with a worse model fit compared to the dTLVC procedure (Zhang et al., 2014). A comparison of the resulting statistical map (Supplementary Material; Fig. S5) to the patient overlap plot (Fig. 1) revealed that especially those areas with the highest lesion frequency across our entire sample were spared out. The regression technique suggested by DeMarco and Turkeltaub (2018) limited the 'searchlight' rather to the border areas of the space of interest. Hence, the regression based control for lesion size appears to generally reduce the amount of significant detections. Indeed, DeMarco and Turkeltaub (2018) noted in their discussion, that the cost of using this technique is a more conservative voxel-wise thresholding. The authors applied SVR-LSM in combination with their lesion volume regression approach on twenty real behavioral scores, but found significant results only in seven of these analyses. This further underlines that lesion volume control by regressing out lesion size from both behavioral and lesion scores, might be excessively conservative in many situations (including the present data). Results using this type of lesion size control thus should be interpreted with caution.

The simulations by Zhang et al. (2014) showed that SVR-LSM is characterized by a good receiver operator characteristic (ROC) performance, especially if lesion-volume correction by dTLVC is included. In

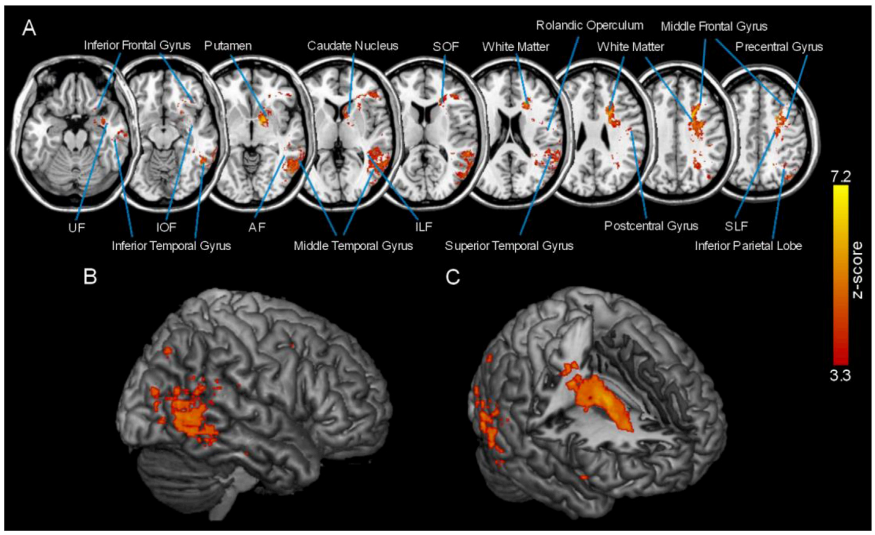

Fig. 4. Results of the univariate lesion behavior mapping using dTLVC. Mass-univariate lesion-symptom mapping results using data of 203 patients. Z-score maps are plotted for VLBM analysis with lesion volume correction by using dTLVC and FDR thresholded at $q = 0.05$, corresponding to a threshold of $z > 3.3828$. Significant clusters were interpreted according to the AAL atlas (Tzourio-Mazoyer et al., 2002) for grey matter regions and to the Juelich probabilistic cytoarchitectonic fiber tract atlas (Bürgel et al., 2006) as well as the tractography-based probabilistic fiber atlas by Thiebaut de Schotten et al. (2011) for white matter structures. B and C: three-dimensional renderings of the same map using the 3D-interpolation algorithm provided by MRIcron (http://people.cas.sc.edu/rorden/mricron/index.html; 8 mm search depth) with sagittal view for B and inside view for C. Results of A, B and C are shown as 1-p. D: Thresholded β-parameter map showing only significant areas according to A. Abbreviations: SLF – superior longitudinal fasciculus; AF – arcuate fasciculus; ILF – inferior longitudinal fasciculus; IOF – inferior occipitofrontal fasciculus; SOF – superior occipitofrontal fasciculus; UF – Uncinate fasciculus.

contrast, ROC characteristics of VLBM were generally worse and thresholds with both good sensitivity and specificity were not available. While Zhang et al. (2014) showed an overall superior performance of the multivariate mapping technique, it might be possible that, in the present investigation, the large sample size contributed to high power amongst various regions. To validate this assumption, it would be necessary to conduct a simulation study using different sample sizes and evaluate how this modification affects results of univariate and multivariate mapping.

Taking all of our univariate findings together, one can conclude that in the framework of multi-area based syndromes, VLBM does not in general fail to detect such networks. Rather, results in lesion symptom mapping can be influenced by the exact choice of analysis parameters (e.g. minimum lesion affection, lesion volume control procedure, and correction for multiple comparisons). In the present study, one of our various VLBM analyses used FDR correction and a very recent procedure for lesion size control, namely dTLVC. By using this type of univariate VLBM analysis, we obtained the same complex network pattern underlying spatial neglect as we revealed it by using a multivariate lesion analysis approach for the same data set. Whether this conclusion also applies to other cognitive deficits and data sets remains to be seen and will have to be investigated in future studies. For the moment, however, we suggest to apply dTLVC rather than the tradional nuisance regression procedure if using a univariate lesion analysis approach. For this purpose we integrated the dTLVC lesion volume correction into the NiiStat tool (https://github.com/neurolabusc/NiiStat) and hence this type of correction can now easily be applied by using this toolbox.

In contrast to our present MLBM findings, two previous multivariate examinations on spatial neglect (Smith et al., 2013; Toba et al., 2017) were able to uncover only parts of the discussed network. Very likely this is due to the small sample size in one of them (Toba et al., 2017) and – most importantly – the very limited number of a priori defined brain regions per multivariate model in both studies. In another recent multivariate investigation using ridge regression (Corbetta et al., 2015), the authors pointed to limitations based on sufficient lesion overlap in some areas which affects ridge regression performance. Hence, they were able to delineate only those parts of the network which were sufficiently sampled. In a similar way, Carter et al. (2017) used ridge regression and reduced their analysis a priori to the right middle cerebral artery territories for their multivariate mapping. In contrast, the present multivariate SVR-LSM analysis as well as our VLBM analysis using the same parameter configurations both utilized voxel-wise information and uncovered a larger set of cortical and subcortical areas, able to account for inconsistencies on the anatomical representation of spatial neglect. The finding highly corresponds to the areas proposed as being part of the 'perisylvian network' representing the anatomical basis for processes involved in spatial orienting and neglect (Karnath and Rorden, 2012), consisting of superior/middle temporal, inferior parietal, ventrolateral frontal cortices as well as their white matter connections. In that context, it is worth mentioning that our Fig. 3A bears a clear resemblance from Fig. 5A from Carter et al. (2017). Both studies have relatively large sample sizes (Carter et al., [2017] tested 70 individuals; the present study tested 203 patients) with continuous measures. However, it is also worth noting that both studies illustrate very different patient behaviors. While our present work directly measured neglected stimuli by using a conventional neglect cancellation task, Carter et al. (2017) used a reaction time measure where responses slower than 2000 ms were excluded. Therefore, the 'field effect' illustrated in their Fig. 5A illustrates slowed responses to perceived stimuli rather than the lack of responses due to truly neglected stimuli.

At the cortical level, lesion location dominantly affected the temporal

Table 3
Detailed overview of all significant grey and white matter clusters – VLBM. Overlap of VLBM analysis with control for lesion size by dTLVC with grey and white matter atlases: FDR correction at $q = 0.05$, corresponding to a threshold of $z > 3.3828$ **(A)**. Overlap of VLBM analysis without control for lesion size with grey and white matter atlases **(B & C). B:** permutation-based FWE correction at $p < 0.05$, corresponding to a threshold of $z > 5.3475$; **C:** FDR correction at $q = 0.05$, corresponding to a threshold of $z > 2.8607$. For grey matter structures, reports are generated using the Automatic Anatomical Labeling atlas (AAL; Tzourio-Mazoyer et al., 2002). For white matter structures, reports are generated using the Juelich probabilistic cytoarchitectonic atlas (Bürgel et al., 2006) and the tractography-based probabilistic fiber atlas by Thiebaut de Schotten et al. (2011) defined at a probability of $p \geq 0.3$. Only structures with at least 100 mm^3 of overlapping voxels were reported in the table. For the VLBM analyses with correction for lesion size, no overlap table is generated, as no clear labeling was possible.

A) FDR- thresholding with dTLVC correction

GM structure (AAL)	Number of voxels (mm^3)	z-score (Mean/SD)	z-score (Peak)
Middle temporal gyrus	7784	3.98/0.51	6.52
Inf. temporal gyrus	3141	4.21/0.56	6.43
Sup. temporal gyrus	1812	3.83/0.35	5.63
Middle. frontal gyrus	883	4.10/0.59	6.23
Angular gyrus	762	3.77/0.34	5.21
Inf. frontal gyrus/triangular	756	3.86/0.31	4.95
Middle occipital gyrus	614	3.85/0.41	5.62
Pallidum	568	4.49/0.89	6.86
Caudate	521	3.92/0.45	5.10
Inf. frontal gyrus/orbital	486	3.82/0.28	4.70
Precentral gyrus	379	3.91/0.44	5.77
Putamen	356	3.77/0.41	5.90
Amygdala	249	3.90/0.41	5.13
Rolandic operculum	188	3.60/0.21	4.43
Sup. temporal pole	181	3.79/0.28	4.67
Supramarginal gyrus	151	3.72/0.28	5.12
Middle temporal pole	146	3.79/0.31	4.98
Inf. occipital gyrus	143	3.93/0.46	5.53

WM structure (Juelich)	Number of voxels (mm^3)	z-score (Mean/SD)	z-score (Peak)
Callosal body	2785	4.44/0.81	7.20
Corticospinal tract	1001	4.04/0.59	6.18
Optic radiation	951	3.77/0.35	5.46
Sup. occipito-frontal fasciculus	236	4.00/0.53	5.60
Sup. Longitudinal fasciculus	120	3.84/0.48	5.47

WM structure (Thiebaut De Schotten)	Number of voxels (mm^3)	z-score (Mean/SD)	z-score (Peak)
Corpus callosum	2909	4.51/0.81	7.20
Internal capsule	2510	4.32/0.85	7.20
Arcuate fasciculus	2293	3.82/0.41	6.22
Posterior segment (Arcuate)	2090	3.84/0.42	6.22
Corticospinal tract	1676	4.27/0.76	6.84
Inf. longitudinal fasciculus	1550	3.85/0.42	6.43
Uncinate	1093	3.79/0.34	5.36
Anterior commissure	1019	4.18/0.72	6.86
Cingulate	916	4.28/0.59	6.25
Inf. occipito-frontal fasciculus	547	3.69/0.23	4.87
Optic radiations	303	3.72/0.27	4.73
Sup. longitudinal fasciculus	238	3.71/0.28	4.50
Anterior segment (Arcuate)	208	3.63/0.21	4.36

B) FWE- thresholding without correction for lesion size

GM structure (AAL)	Number of voxels (mm^3)	z-score (Mean/SD)	z-score (Peak)
Middle temporal gyrus	1304	5.66/0.28	6.86
Pallidum	523	5.93/0.48	7.26
Middle frontal gyrus	438	5.85/0.35	6.96
Inf. frontal gyrus/triangular	391	5.63/0.19	6.05
Putamen	228	5.66/0.33	6.94
Sup. temporal gyrus	167	5.58/0.20	6.23
Caudatum	129	5.57/0.19	6.20
Inf. frontal gyrus/orbital	113	5.60/0.20	6.06
Middle occipital gyrus	113	5.73/0.28	6.55

Table 3 (*continued*)

B) FWE- thresholding without correction for lesion size

WM structure (Juelich)	Number of voxels (mm^3)	z-score (Mean/SD)	z-score (Peak)
Callosal body	1832	6.07/0.53	7.66
Corticospinal tract	544	5.80/0.36	6.75
Sup. occipito-frontal fasciculus	128	5.78/0.37	6.90

WM structure (Thiebaut De Schotten)	Number of voxels (mm^3)	z-score (Mean/SD)	z-score (Peak)
Corpus callosum	2508	6.01/0.52	7.66
Internal capsule	2187	5.97/0.49	7.66
Corticospinal tract	1771	5.89/0.41	7.41
Cingulate	530	5.78/0.34	7.24
Anterior commissure	304	5.97/0.48	7.26
Arcuate fasciculus	269	5.63/0.28	6.58
Posterior segment (Arcuate)	267	5.63/0.28	6.58
Cortico ponto cerebellum	169	5.76/0.34	6.69
Uncinate	126	5.60/0.22	6.36
Inf. longitudinal fasciculus	122	5.63/0.29	6.68
Inf. occipito-frontal fasciculus	100	5.58/0.22	6.36

C) FDR- thresholding without correction for lesion size

GM structure (AAL)	Number of voxels (mm^3)	z-score (Mean/SD)	z-score (Peak)
Middle temporal gyrus	25761	4.03/0.73	6.86
Sup. temporal gyrus	14260	3.68/0.61	6.23
Angular gyrus	8455	3.65/0.52	5.86
Putamen	7628	4.02/0.65	6.94
Insula	7501	3.45/0.40	5.36
Middle occipital gyrus	6529	3.69/0.58	6.55
Inf. temporal gyrus	6374	4.00/0.72	6.72
Inf. frontal gyrus/triangular	5894	3.89/0.77	6.05
Caudatum	5335	4.18/0.59	6.20
Precentral gyrus	5335	3.72/0.64	6.85
Inf. frontal gyrus/opercular	5158	3.47/0.46	5.87
Middle frontal gyrus	5078	4.08/0.81	6.96
Rolandic operculum	4609	3.60/0.54	5.90
Inf. frontal gyrus/orbital	4433	4.02/0.58	6.06
Supramarginal gyrus	4196	3.36/0.40	5.68
Inf. parietal gyrus	2814	3.35/0.38	4.89
Postcentral gyrus	2776	3.31/0.35	5.19
Pallidum	2158	4.87/0.80	7.26
Sup. temporal pole	2123	3.42/0.47	5.61
Amygdala	1351	3.96/0.59	6.12
Hippocampus	1060	3.57/0.58	5.60
Sup. parietal gyrus	704	3.25/0.30	4.72
Thalamus	664	3.42/0.47	5.14
Middle temporal pole	601	3.54/0.53	5.47
Inf. occipital gyrus	392	4.12/0.83	6.50
Olfactory cortex	276	3.62/0.38	4.77
Sup. occipital gyrus	195	3.18/0.26	4.21
Fusiform gyrus	154	3.40/0.45	4.81
Transverse temporal gyrus	139	3.03/0.13	3.48
Sup. frontal gyrus/orbital	103	3.94/0.43	4.86

WM structure (Juelich)	Number of voxels (mm^3)	z-score (Mean/SD)	z-score (Peak)
Corticospinal tract	10278	3.90/0.76	6.75
Corpus callosum	8367	4.40/1.10	7.66
Optic radiation	7702	3.79/0.59	6.64
Sup. longitudinal fasciculus	1925	3.64/0.53	6.11
Inf. occipito-frontal fasciculus	1742	3.72/0.49	5.14
Sup. occipito-frontal fasciculus	1377	4.35/0.75	6.90
Acoustic radiation	794	3.32/0.36	4.68
Uncinate fasciculus	738	3.98/0.46	5.80

WM structure (Thiebaut De Schotten)	Number of voxels (mm^3)	z-score (Mean/SD)	z-score (Peak)
Internal capsule	16030	4.24/0.95	7.66
Arcuate fasciculus	15722	3.91/0.63	6.58
Corticospinal tract	11583	4.23/0.97	7.41
Inf. longitudinal fasciculus	10365	3.80/0.60	6.68
Posterior segment (Arcuate)	9743	4.07/0.65	6.58
Corpus callosum	9737	4.59/1.06	7.66
Inf. occipito-frontal fasciculus	9049	3.84/0.58	6.36

(*continued on next page*)

Table 3 (*continued*)

WM structure (Thiebaut De Schotten)	Number of voxels (mm^3)	z-score (Mean/SD)	z-score (Peak)
Uncinate fasciculus	6650	3.97/0.61	6.36
Anterior segment (Arcuate)	6335	3.63/0.48	5.47
Anterior commissure	3889	4.17/0.79	7.26
Optic radiations	2965	3.84/0.58	5.79
Cingulum	2914	4.38/0.92	7.24
Cortico ponto cerebellar	2607	3.78/0.80	6.69
Fornix	1208	3.47/0.44	5.18
Sup. longitudinal fasciculus	1205	3.78/0.52	5.35
Long segment (Arcuate)	691	3.58/0.44	5.02

cortex and its borders into inferior parietal and occipital cortices (cf. Figs. 3 and 4). The right temporal lobe has been delineated in previous lesion mapping studies in spatial neglect (Karnath et al., 2001, 2004; 2011; Committeri et al., 2007; Saj et al., 2012; Rousseaux et al., 2015). Smith et al. (2013) found the superior temporal gyrus (STG) as being the only structure which contained unique information for predicting spatial neglect. Accordingly, the STG seems to play an important role in multisensory integration, conveying information from both, the dorsal route of visual information processing, as well as polysensory inputs from the ventral perceptual stream (for review, see Karnath et al., 2001). Further evidence for the importance of superior/middle temporal areas for spatial neglect comes from recent animal models (Bogadhi et al., 2019). The authors detected a causal relationship between spatial neglect like symptoms and the superior temporal sulcus by direct and indirect 'inactivation' of that area in the monkey brain, underlining it's crucial role in covert attentional processing. In the human brain, the posterior part of the STG at the intersection to the inferior parietal cortex, an area which is called 'temporo-parietal junction' (TPJ) (Chang et al., 2013; Kincade et al., 2005; Macaluso and Doricchi, 2013) together with the ventral frontal cortex (VFC) (Corbetta and Shulman, 2002; Snyder and Chatterjee, 2006) have been reported as target areas for attentional reorienting, target detection and vigilance (Corbetta and Shulman, 2011). Lesions in these cortical areas, together with white matter disconnection hindering the information transmission between them (see below), seem to form the basis for the core deficit observed in spatial neglect patients.

The superior longitudinal fasciculus connects the ventral frontal cortex to parietal structures via different sub-branches, the SLF I, SLF II and SLF III, identified in both humans, and monkeys (Schmahmann and Pandya, 2006; Thiebaut de Schotten et al., 2011). The SLF has repeatedly been

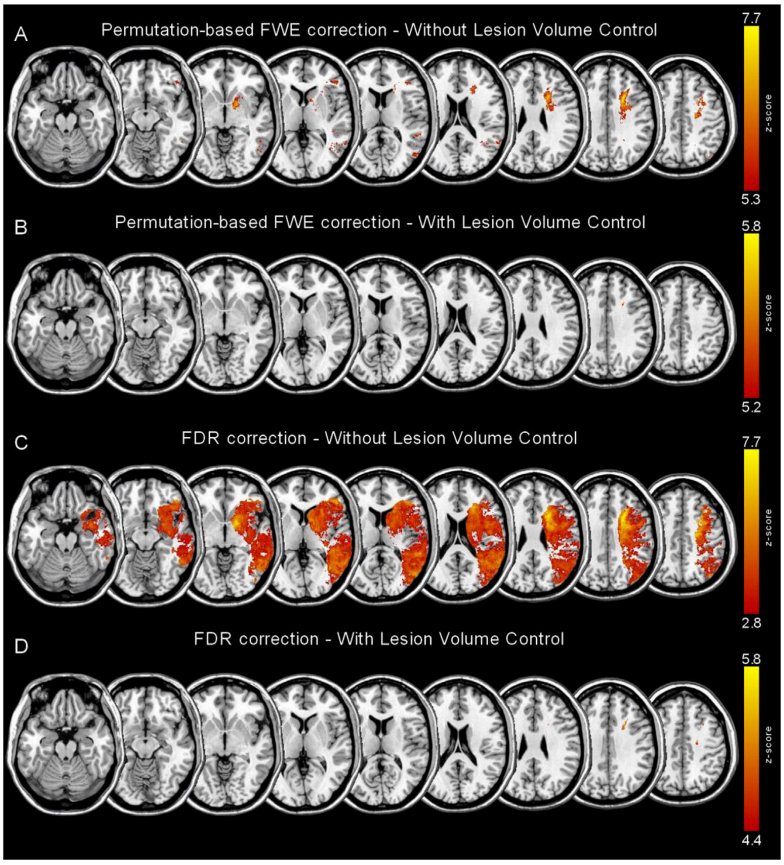

Fig. 5. Results of all further univariate lesion behavior mapping analyses. Mass-univariate lesion-symptom mapping results using data of 203 patients. Z-score maps are plotted for FWE permutation-thresholded as well as FDR-thresholded VLBM analyses with and without lesion volume correction on CoC scores. A: FWE permutation thresholded VLBM analysis without correction for lesion size at $p < 0.05$, corresponding to a threshold of $z > 5.3475$; B: FWE permutation thresholded VLBM analysis with correction for lesion size – by regressing lesion size out of behavior – at $p < 0.05$, corresponding to a threshold of $z > 5.2251$; C: FDR thresholded VLBM analysis without correction for lesion size at $q = 0.05$, corresponding to a threshold of $z > 2.8607$; D: FDR thresholded VLBM analysis with correction for lesion size – by regressing lesion size out of behavior – at $q = 0.05$, corresponding to a threshold of $z > 4.4772$.

discussed as being a crucial fronto-parietal pathway for processes of attentional orienting (Corbetta and Shulman, 2002; Bartolomeo et al., 2007). The ventral branch of the SLF (SLF III) specifically connects brain regions within the ventral attention network (VAN) (Rushworth et al., 2006; Bartolomeo et al., 2012; Thiebaut de Schotten et al., 2011) engaged in the propagation of information of stimulus identity and during the automatic capture of spatial attention by visual targets (Corbetta and Shulman, 2002). A further intrahemispheric tract partly overlapping with the SLF and confirmed in the present investigation is the arcuate fasciculus (AF). The AF is sometimes considered as an additional subcomponent of the SLF (Makris et al., 2005; Vernooij et al., 2007) and has been discussed in the transmission of information related to visuospatial performance (Chechlacz et al., 2014; Ciaraffa et al., 2013; Thiebaut De Schotten et al., 2014). This fiber bundle is composed of long and short anterior as well as short posterior fibers connecting specifically perisylvian frontal, parietal and temporal areas (Catani and Thiebaut de Schotten, 2008). Additionally, our results indicate the crucial involvement of the occipitofrontal fasciculus (IOF) – also termed as 'inferior frontooccipital fasciculus' (IFOF) –, which runs through the temporal lobe medial to the lower insula and connects areas of the frontal cortex with posterior temporal, inferior parietal, and occipital cortices (Nieuwenhuys et al., 1988; Catani et al., 2002; Bürgel et al., 2006; Forkel et al., 2014; Lawes et al., 2008). It has been suggested, that damage of this tract may hamper the transmission and/or the serial encoding of visual information in memory (Humphreys et al., 2015). This might explain deficits in target/distractor discriminative cancellation tasks, whereas no specific link between the IOF on line cancellation without distractor items has been reported (Urbanski et al., 2008). Our analysis depicted also the inferior longitudinal fasciculus (ILF), a further association tract connecting temporal to occipital areas (Catani et al., 2008), which has been linked previously to spatial neglect (Bird et al., 2006; Toba et al., 2018).

The present analysis also observed significant clusters subcortically for the right basal ganglia, including putamen, pallidum, and caudate nucleus. Based on previous work using perfusion imaging to monitor the remote effects of subcortical lesions (e.g. Hillis et al., 2002; Karnath et al., 2005), it is very likely that lesions of the basal ganglia lead to behavioral dysfunction by impairing the cortical network indirectly by malperfusion. However, there might also be a direct involvement of the basal ganglia. A recent simulation study by Parr and Friston (2018) aimed to formulate spatial neglect as a computational deficit. By setting up a model structure corresponding to the anatomy of dorsal and ventral attention networks, as well as their subcortical contributions, they demonstrated that basal ganglia lesions can directly produce neglect behavior in a saccadic cancellation task.

Interestingly, we also found significant clusters in areas and fibers typically associated with primary visual field defects (occipital gyri, optic radiation). Indeed, in our experiment, patients with visual field defects were not excluded from the analysis. The rationale for this follows two purposes. First, patients with visual field defects will probably have a more posterior lesion. Excluding such patients systematically from the analysis (or considering this as a co-variable of no interest) could produce an unwanted anatomical bias, namely an artificially created shift towards and increased power for detecting more anterior brain regions. Secondly, previous investigations have shown that visual field defects do not exacerbate neglect-specific symptoms in exploration tasks (e.g., Halligan et al., 1990). In agreement with such findings, the presence or absence of visual field defects was not significantly correlated with the patients' CoC scores ($r = 0.15$, n.s.). Finally, it might be possible that in a particular number of patients of our sample there is a co-occurrence of lesion patterns that alter a neglect-specific anatomical module but also spreading over to more posterior areas and fiber tracts associated with primary visual field defects. Thus, it is possible that in lesion mapping these areas will become significant although they are not directly involved in neglect behavior. This might also explain why the correlation between primary visual field defects and the CoC score was not significant and why we observed patients with primary visual field defects among those with as well as without spatial neglect.

Summarizing our anatomical results, multivariate and univariate lesion behavior mapping were able to depict the network by using only the CoC score as behavioral proxy for spatial neglect and attention, whereas previous studies have employed either a meta-analytical (Checlacz et al., 2012; Molenberghs et al., 2012), multi-imaging/multi-method (Corbetta et al., 2015; Ramsey et al., 2016), or ROI approaches (Smith et al., 2013) to increase power or to disentangle the behavioral sub-functions and map them separately (Verdon et al., 2010; Vaessen et al., 2016; Toba et al., 2018) to come to comparable conclusions. This indicates that the behavioral proxy we measured here is indeed a core symptom of spatial neglect as it might evolve regardless where within this network a lesion produces focal dysfunction or remote deficits through disconnection. Nevertheless, we want to emphasize that future studies might apply the same analysis procedures used here for the core symptom of spatial neglect to uncover the neural underpinnings of the dissociating spatial and non-spatial behaviors. To disentangle the different components, these behavioral tasks in such future studies should be as fine graded as possible to detect a specific cognitive function in isolation (for discussion, see Sperber and Karnath, 2018; Vuilleumier, 2013; Saj et al., 2012).

5. Conclusion

The comparison between univariate and multivariate lesion analysis techniques revealed that spatial maps corresponded with each other if the exact same correction factors and parameter combinations (FDR correction and dTLVC for lesion size control) were used. Both approaches uncovered a complex network pattern underlying spatial neglect (though SVR-LSM was able to provide a better overall model fit throughout the statistically significant areas). Our findings underline the importance of a right network in spatial exploration and attention and specifically in the emergence of the core symptoms of spatial neglect. A remaining task for future studies is to investigate if the SVR-LSM approach employed here is indeed the most suitable multivariate analysis technique for studying the type of research question addressed in the present study. A comparison of different multivariate algorithms in multivariate lesion-behavior mapping as well as the evaluation of the impact of varying sample sizes in the comparison between univariate and multivariate mapping are needed.

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Appendix A. Supplementary data

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Using machine learning-based lesion behavior mapping to identify anatomical networks of cognitive dysfunction: spatial neglect and attention

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Supplementary Material

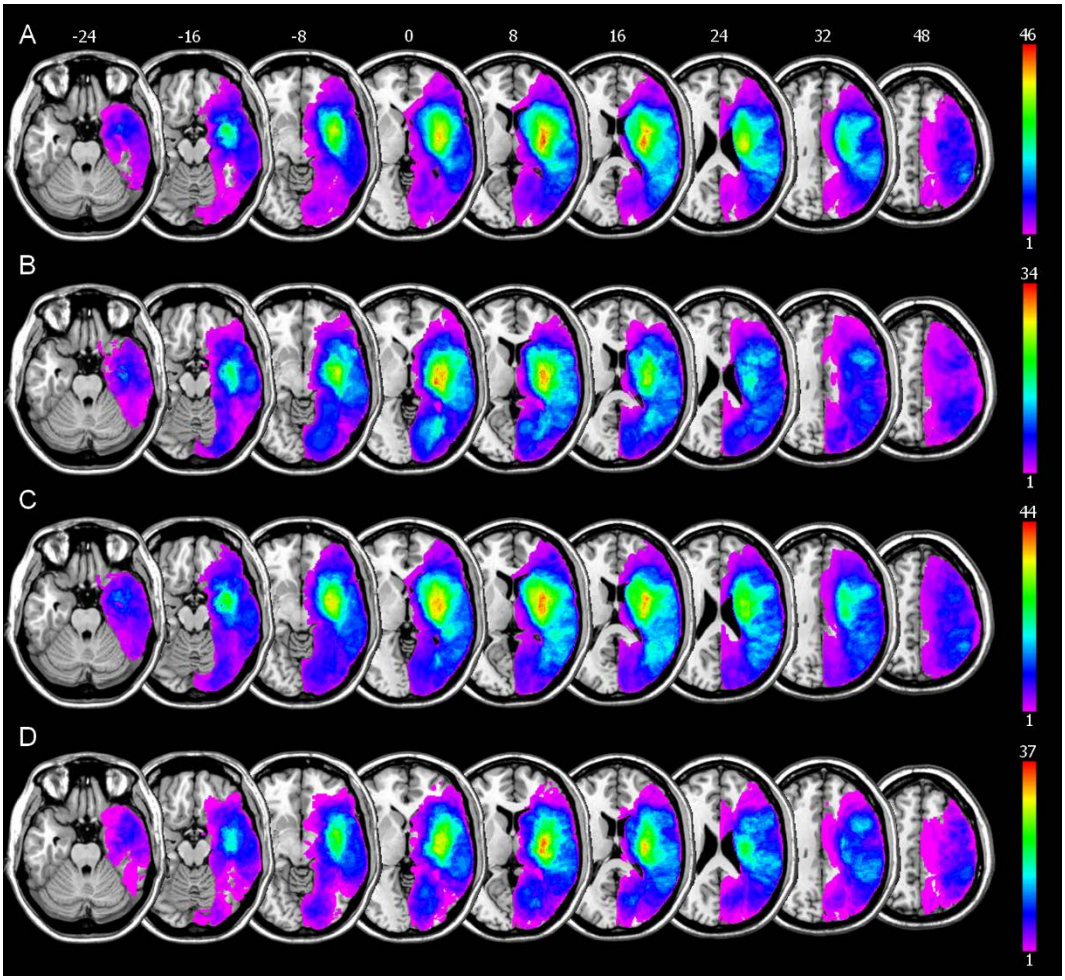

Figure S1: Topography of brain lesions

A: Lesion overlap topography of all lesions defined by MR (N = 106). **B:** Lesion overlap topography of all lesions defined by CT (N = 97). **C:** Lesion overlap topography of all lesions of patients with spatial neglect diagnosis (N = 81). **D:** Lesion overlap topography of all lesions of patients without spatial neglect diagnosis (N = 122). The colorbar indicates the number of overlapping lesions with peak at N = 46 for MR (i.e. 43% affection of all MR delineated lesions at peak), N = 34 for CT (i.e. 35% affection

of all CT delineated lesions at peak), N = 44 for patients with spatial neglect diagnosis (i.e. 54% affection of all lesions of patients with spatial neglect diagnosis at peak), N = 37 for patients without spatial neglect diagnosis (i.e. 30% affection of all lesions of patients without spatial neglect diagnosis at peak). Numbers above the slices indicate z-coordinates in MNI space.

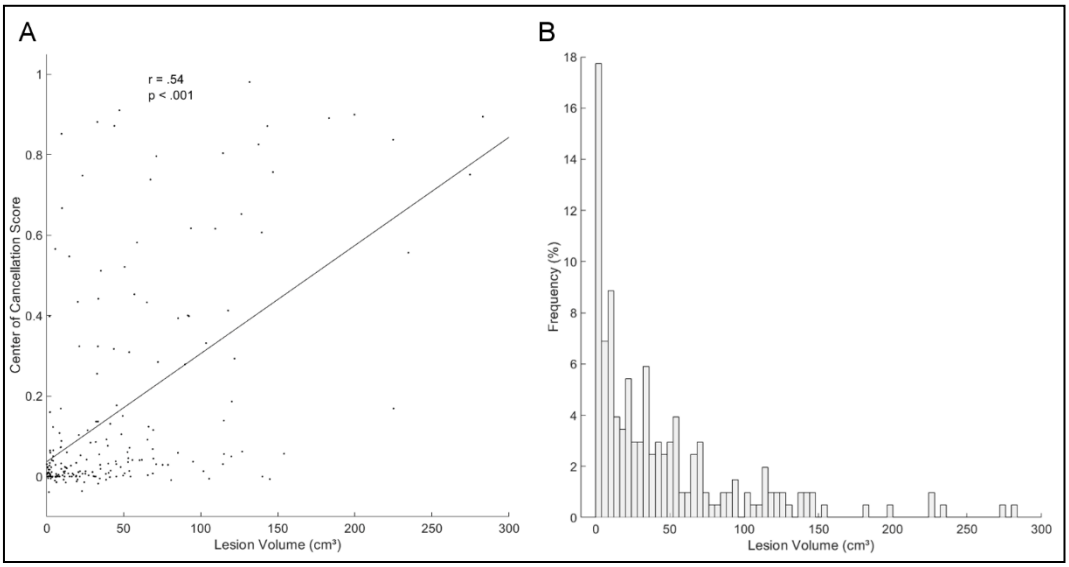

Figure S2: Lesion volume distribution and correlation between lesion volume and the behavioral score

A: Correlation between lesion volume and Center of Cancellation score. **B:** Lesion volume distribution over all 203 patients.

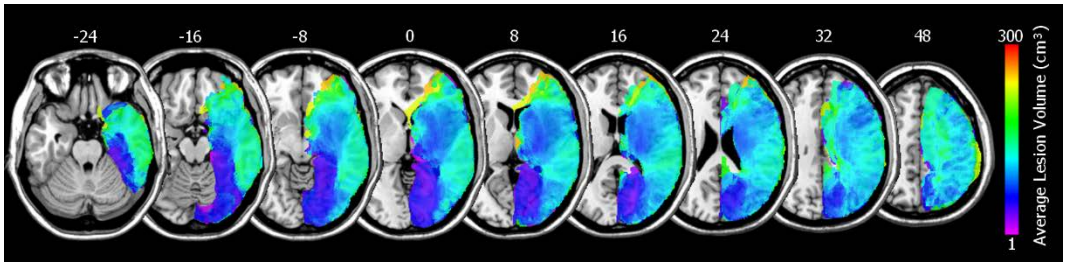

Figure S3: Average Lesion Volume per voxel

Figure showing the regional bias introduced by lesion volume in the complete sample of 203 patients. The average lesion volume has been calculated for each voxel and is shown as cm^3.

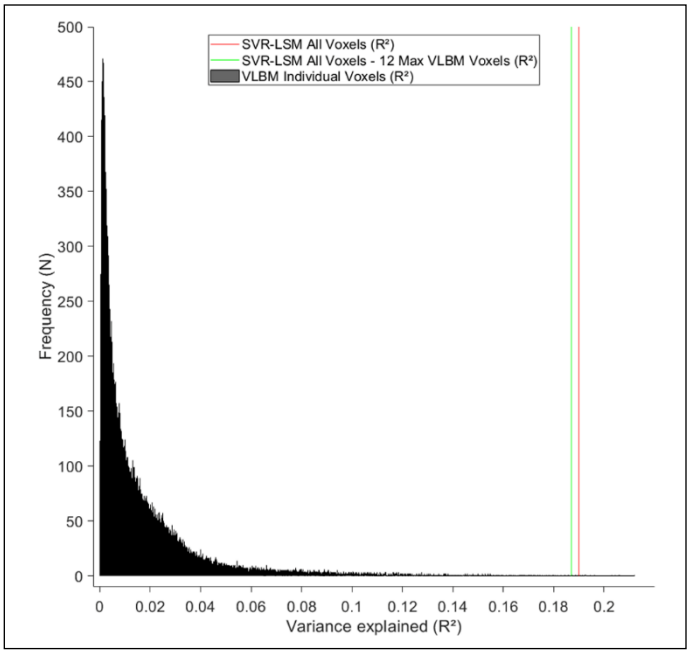

Figure S4: Distribution of R^2 values for VLBM and SVR-LSM

Figure showing the distribution of R^2 values for each individual voxel in VLBM (Black), as well as the model specific R^2 for SVR-LSM using all voxels (Red). The SVR-LSM model yields an R^2 of 0.19. 12 voxels of the VLBM analysis are exceeding this threshold. A further evaluation shows the model specific R^2 for SVR-LSM without the 12 VLBM voxels exceeding the R^2 of 0.19 (Green). Model fits for VLBM and SVR-LSM have been extracted by taking the 5-fold cross-validation R^2 (averaged over runs and folds from a repeated 5-fold cross-validation scheme). All models have been calculated after using dTLVC to correct for lesion volume effects.

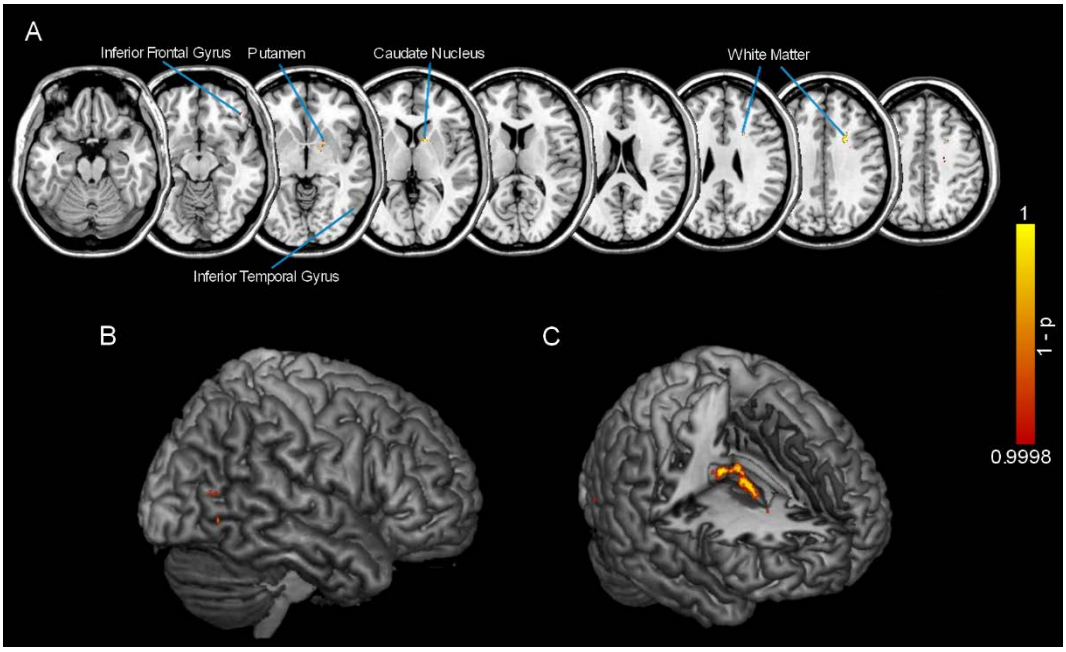

Figure S5: Results of the multivariate lesion-behavior mapping controlled for lesion size by regression out of behavior and lesion

Support vector regression based multivariate lesion-symptom mapping results using data of 203 patients. Lesion volume correction was performed by regressing lesion volume out of both behavioral and lesion scores (DeMarco and Turkeltaub, 2018). **A:** Permutation-thresholded statistical map of SVR-LSM on CoC scores (FDR-corrected at $q = 0.05$, corresponding to a threshold of $p < 0.0002$), illustrating the anatomical regions significantly associated with the core deficit of spatial neglect. Significant clusters were interpreted according to the AAL atlas (Tzourio-Mazoyer et al., 2002) for grey matter regions and to the Juelich probabilistic cytoarchitectonic fiber tract atlas (Bürgel et al., 2006) as well as the tractography-based probabilistic fiber atlas (Thiebaut De Schotten et al., 2011) for white matter structures. **B and C:** three-dimensional renderings of the same map using the 3D-interpolation algorithm provided by MRIcron (http://people.cas.sc.edu/rorden/mricron/index.html; 8mm search depth) with sagittal view for **B** and **C**. Results are shown as 1-p.

Structural (Dis)Connectomics of spatial exploration and attention: a study of stroke patients with spatial neglect

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Abstract

Spatial attention and exploration are related to a predominantly right hemispheric network structure. However, areas of the brain involved and the exact role they might have is still controversially discussed. Spatial neglect following right hemispheric stroke lesions has been frequently viewed as a model to study these processes in humans. Previous investigations on the anatomical basis on spatial neglect predominantly focused on focal brain damage and lesion-behaviour mapping analyses. This approach might not be suited to detect remote areas structurally spared but which might contribute to the behavioural deficit. In the present study of a sample of 203 right hemispheric stroke patients, we combined connectome lesion-symptom mapping with multivariate support vector regression to unravel the complex and disconnected network structure in spatial neglect. We delineated three central nodes that were extensively disconnected from other intrahemispheric areas, namely the right superior parietal lobule, the insula, and the temporal pole. Additionally, the analysis allocated central roles within this network to the inferior frontal gyrus (pars triangularis and opercularis), right middle temporal gyrus, right temporal pole and left and right orbitofrontal cortices, including interhemispheric disconnection. Our results suggest that these structures – although not necessarily directly damaged – might play a role within the network underlying spatial neglect in humans.

Keywords: Spatial neglect; attention; structural; CLSM; SVR-LSM; stroke

Introduction

Spatial neglect is one of the most common behavioural consequences after brain injury of predominantly the right hemisphere (Becker and Karnath, 2007; Stone et al., 1993; Ten Brink et al., 2017). It is considered to affect tasks of spatial attention and orientation (Corbetta et al., 2008, 2005; Karnath, 2015). Spatial neglect patients typically deviate towards the ipsilesional side, neglecting contralesionally located information or stimuli (Heilman et al., 1983; Karnath and Rorden, 2012). The disorder is evoked by affection of (parts of) a right perisylvian anatomical network, involving frontal, parietal and temporal grey matter areas and interconnecting white matter fibres (Karnath and Rorden, 2012; Wiesen et al., 2019). Evidence for a large-scale network in spatial neglect also comes from Parr and Friston (2018) who developed a computational model of attention based on active inference and induced symptoms of spatial neglect by virtually lesioning distinct nodes of this network (i.e. nodes of dorsal and ventral attention networks and contributions of the basal ganglia). Correspondingly, Bogadhi et al. (2019) found direct causal evidence in the monkey brain, that the direct and indirect inactivation of crucial hubs of the network produces neglect-like lateralised deficits.

So far, most of the previous anatomical investigations of spatial neglect used methods such as univariate or multivariate lesion-symptom mapping (e.g. Bates et al., 2003; Rorden et al., 2007; Wiesen et al., 2019). What these methods have in common is that they test areas directly affected by brain lesions. Beyond, focal lesions also may produce remote dysfunctions due to malperfusion or disconnection in areas that are structurally intact. Disruption of such areas might contribute to the behavioural deficit. Thus, it appears essential to integrate information about structural disconnection in anatomo-functional models on brain function.

In the past, methods for the evaluation of remote structural and functional effects of brain damage in neurological patients have included perfusion weighted imaging (PWI), diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI), and resting state functional magnetic resonance imaging (rfMRI) (for a recent overview, see Karnath et al., 2018). Typically, these methods require to collect imaging data directly in patient samples. However multimodal brain imaging is typically not acquired in clinical routine imaging protocols and needs to be collected additionally with much effort in neurological patients, in order to answer research questions. Especially in the acute phase of stroke, this can raise ethical questions that are difficult

to resolve. A further way to capture remote effects of stroke lesions is to use large databases of normative connectome data to approximate effects real lesions might have on network dynamics. These datasets can be based on functional as well as structural imaging and lead to the development of new techniques and tools, such as disconnection-symptom mapping (DSM; Foulon et al., 2018; Wiesen et al., 2020) or connectome lesion-symptom mapping (CLSM; Del Gaizo et al., 2017; Yourganov et al., 2016). Salvalaggio et al. (2020) found that especially information from such structural disconnection was predictive for most of the behavioural variables investigated, whereas information from indirect functional disconnection was not. Connectome based lesion-symptom mapping is also especially appealing, as it is the first analysis approach directly linking white matter disruption to high resolution grey matter nodes, providing a large scale perspective on structural network organization and dynamics selectively impaired in patient samples (see Gleichgerrcht et al., 2017). In the present investigation, we aimed to use a multivariate connectome lesion-symptom mapping approach to detect critical hubs in right brain damaged patients, specifically related to the severity of spatial neglect. We expected that information from such an analysis can provide valuable insights into brain functioning, complementing research in the field of lesion-symptom mapping (Karnath et al., 2018).

Methods

Patient recruitment

The sample consisted of 203 neurological subjects admitted to the Centre of Neurology at Tuebingen University, which participated already in a previous investigation (Wiesen et al., 2019). Patients were screened for a first ever right-hemisphere stroke, exclusion criteria included the presence of diffuse or bilateral brain lesions, patients with tumours and patients in whom MRI or CT scans revealed no obvious lesions. Table 1 shows demographic and clinical data. Subjects gave their informed consent to participate in the study, which was performed in accordance with the ethical standards laid down in the revised Declaration of Helsinki and with local guidelines and regulations of the University Hospital Tuebingen.

Table 1: Demographic and clinical data of the 203 patients included.

For this table we determined whether a CoC (= Center of Cancellation; see Rorden and Karnath, 2010) score was in the pathological range; cut-offs were set at >.083 for the

Letter Cancellation test and >.081 for the Bells Cancellation Task (cf. Rorden and Karnath, 2010). A positive diagnosis of spatial neglect was assigned if a pathological test score in at least one of the two cancellation tests was detectable. 122 (60%) did not exhibit neglect, while 81 (40%) were classified as exhibiting spatial neglect. Data are represented as mean (SD). Note that in the statistical tests we treated the severity as a continuous measure. The table reveals that using cut-off threshold, there is little variability in patients without pathological bias (ceiling performance). In contrast symptom severity varies across patients with pathological deficits. Modified from Wiesen et al. (2019).

	No neglect	Neglect
Sex (F/M)	51/71	33/48
Age (years)	60.2 (13.7)	64.7 (12.4)
Visual Field Defects (% present)	14	27
Time since lesion (days)	3.2 (4.5)	4.2 (4.3)
Imaging (CT/MRI)	53/69	44/37
Etiology (Hemorrhage/Ischemia)	18/104	12/69
Lesion size (cm^3)	29.3 (35.0)	70.0 (64.4)
Letter Cancellation (CoC)	0.01 (0.02)	0.36 (0.32)
Bells Cancellation (CoC)	0.01 (0.03)	0.39 (0.29)

Neuropsychological examination

To evaluate the presence of spatial neglect, patients underwent a test routine including the Letter Cancellation Task (Weintraub and Mesulam, 1985) and Bells Test (Gauthier et al., 1989). The centre of a 21x29.7 cm sheet of paper including the Bells- or Letter-task was aligned with the patient´s sagittal midline. Partients were instructed to either cancel out among distractors 60 target 'A' letters (for the letter cancellation task) or 35 bell icons (for the Bells cancellation task), distributed over the sheet. There was no time limit; patients decided on their own about the end of the tasks. Patients' own satisfaction of the performance was checked twice by the investigator. To get a stable estimate of the severity of the neglect typical bias, we first calculated the Center of Cancellation (CoC) using the procedure suggested by Rorden and Karnath (2010). In a final step, we averaged the two cancellation CoC scores to a compound estimate. The interval

between stroke-onset and neuropsychological examination was maximally 25 days (mean = 4.37 days, SD = 4.04). Visual field defects were examined by the common neurological confrontation technique.

Imaging

Structural imaging was acquired either by MRI (n = 106) or CT (n = 97), performed on average 3.5 days (SD = 4.6) after stroke-onset. MR scans were preferred if both imaging modalities were available. In participants where MR scans were available, we used diffusion-weighted imaging (DWI) if the images were acquired within 48 h after stroke onset or T2-weighted fluid attenuated inversion recovery (FLAIR) images for later scans. Lesion boundaries were manually marked on the transversal slices of the individual MR or CT scans using the free MRIcron software (www.mccauslandcenter.sc.edu/mricro/mricron). Normalization of CT or MR scans to MNI space with 1x1x1 mm resolution was performed by using the Clinical Toolbox (Rorden et al., 2012) under SPM8 (www.fil.ion.ucl.ac.uk/spm), and by registering lesions to its age-specific templates oriented in MNI space for both CT and MR scans (Rorden et al., 2012). If available, MR scans were co-registered with a high resolution T1-weighted structural scan in the normalization process. Delineation of lesion borders and quality of normalization were verified by consensus of always two experienced investigators (one of them H.-O.K.). The average lesion size in the sample was 45.5 cm^3 (SD = 52.7 cm^3). Overlap plots of all normalized lesions and all normalized lesions separated for each imaging modality together with a histogram of the lesion size distribution can be found in the previously published work (Wiesen et al., 2019). Moreover, a figure showing the regional bias caused by lesion volume is shown in the same published work.

Preprocessing of the link-wise structural (dis)connectome

To evaluate structural disconnection, we calculated the white matter link-wise disconnectome, quantifying the amount of disconnection between any two grey matter ROI´s based on individual lesions. The ROI´s were derived based on grey matter areas parcellated in the Desikan-Killiany atlas (Desikan et al., 2006), provided by the IIT Human Brain Atlas (v.5.0) (https://www.nitrc.org/projects/iit/; Zhang & Arfanakis, 2018). All 84 atlas areas were included.

In a first step, we aimed to create a whole brain tractogram. This was based on healthy subjects (i.e. normative data). We used the Spherical harmonic (SH) coefficients of the provided HARDI template (*IIT_HARDI.nii*), including fibre orientation distributions (FOD). All fibre tractography steps were carried out by the tractography package MRtrix3 (https://www.mrtrix.org/; Tournier et al., 2012). To create the whole brain tractogram, we first prepared a seeding mask for performing anatomically constrained tractography (ACT; Smith et al., 2012) by using the *5tt2gmwmi* command in MRtrix3 on the 5 tissue type segmented anatomical image (*IIT_fornix_fixed_5tt_file_for_ACT_tractography.nii*), which was provided by the IIT Human Brain Atlas (v.5.0). This increases the biological plausibility of downstream streamline creation by improving the accurate determination of where streamlines should be terminated (Smith et al., 2012). Then, we generated streamlines using the *tckgen* command with the default *iFOD2* (Second-order Integration over Fiber Orientation Distributions; Tournier et al., 2010) probabilistic algorithm, anatomical constrained deconvolution, seeding 10 million streamlines at the grey matter – white matter boundary and by using *backtrack* (Smith et al., 2012) to allow tracks to be truncated and re-tracked if a poor structural termination is encountered. Next, we down-filtered the tractogram from 10 million to ~1.5 million streamlines, such that the streamline densities match the FOD lobe integrals, by using the SIFT (Spherical-Deconvolution Informed Filtering of Tracks) algorithm (Smith et al., 2013b) . This reduces the constrained spherical deconvolution-based bias in overestimation of longer tracks compared to shorter tracks. In general, by using this filtering procedure, the number of streamlines connecting two regions becomes a proportional estimate of the cross-sectional area of the fibres connecting those two regions, increasing again the biological accuracy of the tractogram.

In a second step, we estimated the 'healthy' normative connectome based on the whole brain tractogram from the previous step with respect to the cortical parcellation of the atlas file (*IIT_GM_Desikan_atlas.nii*). All subsequent preprocessing steps were carried out with MATLAB 2018b. We read in the coordinates of each individual tract into a vector and quantified for any two ROI´s of the parcellation the number of tracks connecting them. As we performed fibre tracking by using ACT, the precise location of streamline termination did not automatically overlap perfectly with the borders of the parcellation of the Desikan atlas (Desikan et al., 2006). Hence, a radial search of 2 mm radius was performed at each streamline start and termination point, to find the

nearest grey matter label. Although we ensured that streamlines start and end at the GM/WM boundaries and connecting one area to another, we further controlled for any inaccuracies during tract reconstruction and discarded streamlines running through 3 or more ROI´s from the tractogram, before deriving the connectome.

We then registered each lesion to the stereotaxic atlas space, discarded for each patient tracks running through the lesion and repeated the above procedure for connectome generation by creating for each patient a connectome matrix with spared ROI-to-ROI connections. As we were interested especially in disconnected links, we subtracted each link of the 'healthy' normative whole brain connectome file by the corresponding link of the respective spared patient connectome, extracting an 84x84 matrix per patient reflecting the link-wise (i.e., ROI-to-ROI) disconnectome. In practical terms, this corresponds to the number of tracks running through any two Desikan atlas ROI´s and disconnected by the lesion. From this matrix, we extracted a subnetwork retaining only links altered in at least one patient and discarded reciprocal connections. Finally, for each patient a row vector of right intrahemispheric and interhemispheric links is then used for the subsequent multivariate connectome lesion-symptom mapping analysis.

SVR-CLSM analysis

Our statistical analysis was performed with a multivariate method that recently gained popularity in the field of lesion-symptom mapping, namely SVR-LSM (Support Vector Regression based Lesion Symptom Mapping; Zhang et al., 2014a). Support vector regression is a supervised machine learning technique (Cortes and Vapnik, 1995; Drucker et al., 1996) which is able to model the continuous relationship between lesion data and behavioural scores. This method was used and validated successfully in previous investigations with real lesion-symptom data (e.g. Sperber et al., 2019a; Wiesen et al., 2019) or synthetic features (e.g. Sperber et al., 2019b). For a detailed description about this method, we refer to the original study by Zhang et al. (2014a). Using this same procedure, but with disconnectome matrices instead of traditional lesion maps, we performed support vector regression based connectome lesion-symptom mapping (SVR-CLSM).

All the analyses were performed with MATLAB 2018b and libSVM 3.23 (Chang and Lin, 2013), using a linear Kernel. A parameter optimization procedure via

grid search was carried out with 5-fold cross-validations to find the C model parameter (search range of $C = 2^{-30}$ - 2^{30} in steps of 1) with the best trade-off between prediction accuracy and reproducibility, similar to the procedure of a previous investigation (Wiesen et al., 2020). In the present experiment, the optimization procedure resulted in empirically optimized values for the model parameter $C = 2^{-17}$. The optimized C was then used in the final SVR-CLSM analysis. During this analysis, we derive SVR β-parameters for each voxel as described by Zhang et al. (2014b), reflecting the model weight (i.e. strength) between structural disconnection of any two ROIs and the mean CoC score. These β-parameters were then tested in a link-wise permutation algorithm to assess statistical significance by 10000 permutations. Results for the SVR-CLSM are shown at $p < 0.0005$ after Bonferroni correction for multiple comparisons. Significant links were interpreted and labelled according to the parcellated ROI´s of the Desikan-Killiany atlas (Desikan et al., 2006).

Results

Parameter optimization

To find the best C parameter for the SVR-CLSM analysis, we ran a 5 times 5-fold cross-validation routine. This resulted in an average prediction accuracy of $r = 0.46$ ($R^2 = 0.21$) with $C = 2^{-17}$, which was used in the final analysis.

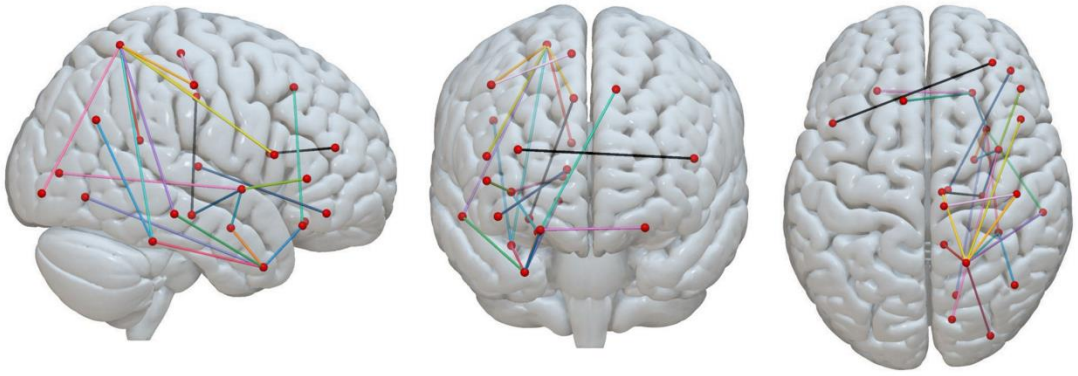
Structural (Dis)connectome analysis

Fig. 1 shows all disconnected links significantly related to higher CoC scores. To facilitate interpretation of the results, we segmented the resulting disconnection network map into subnetworks, depending on whether there were continuous links between nodes or not. Within the first component, we extracted three main right hemispheric hubs with disconnections to > 3 other areas of the brain (cf. Fig. 2), the right superior parietal lobule (7 ROI-to-ROI disconnections), the right insula (4 ROI-to-ROI disconnections), and the right temporal pole (5 ROI-to-ROI disconnections). Although we evaluated only direct links (i.e. no secondary or tertiary disconnections), it is important to note, that the disconnection profile of all damaged links as a whole (i.e. whole network) contributed to the prediction of the behavioural symptom.

Within the first component (cf. Fig. 2), we found in patients with higher impairment, i.e. higher CoC scores, disconnection in the right hemisphere between the

superior parietal lobule (SPL) and the fusiform gyrus, SPL and the inferior frontal gyrus (pars opercularis), SPL and the posterior part of the cingulate cortex, SPL and the isthmus of the cingulate cortex, SPL and the lateral area of the occipital gyrus and between SPL and the middle temporal gyrus. A second important hub within the first component was identified as the right insula. In patients with higher impairment (higher CoC scores), we found higher inter-regional disconnection in the right hemisphere between insula and hippocampus, insula and amygdala, insula and the inferior frontal gyrus (pars triangularis), and between insula and the pericalcarine area in the occipital lobule. The third hub of the first component constituted the right temporal pole (TP) with inter-regional disconnections specifically between the TP and lateral orbito-frontal cortex, TP and middle temporal gyrus, TP and amygdala, TP and fusiform gyrus, and between the TP and the lingual gyrus. Within the first component, additional structural disconnection between the right fusiform gyrus and the right inferior parietal gyrus, the right posterior cingulate and right hippocampus, the lateral part of the right orbito-frontal cortex and the left superior frontal gyrus and between the lateral part of the right orbito-frontal cortex and the lateral part of the left orbito-frontal cortex were related to higher CoC scores.

Components two, three and four were characterized by single ROI-to-ROI disconnections (i.e. structurally not related to other areas of the brain in our analysis) associated to spatial neglect. Component two shows that the link between the right thalamus and the right inferior frontal gyrus (pars orbitalis) was affected. Component three shows that disconnection between the right postcentral gyrus and right paracentral gyrus might be important. Finally, component four identified an interhemispheric disconnection between the rostral section of the right middle frontal gyrus and the left inferior frontal gyrus (pars opercularis).



GM Label 1		GM Label 2	β-Weight
ctx-rh-insula	↔	Right-Hippocampus	10
ctx-rh-temporalpole	↔	ctx-rh-lateralorbitofrontal	8.44
ctx-rh-inferiorparietal	↔	ctx-rh-fusiform	5.67
ctx-rh-insula	↔	Right-Amygdala	4.25
ctx-rh-superiorparietal	↔	ctx-rh-fusiform	3.43
ctx-rh-lateralorbitofrontal	↔	ctx-lh-superiorfrontal	2.86
ctx-rh-temporalpole	↔	ctx-rh-middletemporal	2.25
ctx-rh-insula	↔	ctx-rh-parstriangularis	2.03
ctx-rh-superiorparietal	↔	ctx-rh-parsopercularis	1.15
ctx-rh-superiorparietal	↔	ctx-rh-posteriorcingulate	1.06
ctx-rh-superiorparietal	↔	ctx-rh-postcentral	0.62
ctx-rh-temporalpole	↔	Right-Amygdala	0.56
ctx-rh-superiorparietal	↔	ctx-rh-isthmuscingulate	0.54
ctx-rh-temporalpole	↔	ctx-rh-fusiform	0.30
ctx-rh-superiorparietal	↔	ctx-rh-lateraloccipital	0.27
ctx-rh-insula	↔	ctx-rh-pericalcarine	0.14
ctx-rh-lateralorbitofrontal	↔	ctx-lh-lateralorbitofrontal	0.14
ctx-rh-superiorparietal	↔	ctx-rh-middletemporal	0.14
ctx-rh-temporalpole	↔	ctx-rh-lingual	0.08
ctx-rh-parsorbitalis	↔	Right-Thalamus-Proper	0.07
ctx-rh-posteriorcingulate	↔	Right-Hippocampus	0.02
ctx-rh-postcentral	↔	ctx-rh-paracentral	0.02
ctx-rh-rostralmiddlefrontal	↔	ctx-lh-parsopercularis	0.01

Figure 1: Results of the SVR-CLSM analysis

Support vector regression based connectome lesion-symptom mapping results using data of 203 patients. Permutation-thresholded statistical map of SVR-CLSM on CoC scores (Bonferroni corrected for multiple comparisons after 10000 permutations, corresponding to a threshold of $p < 0.0005$) illustrating anatomical regions disconnected to other brain regions which are related to the core deficit of spatial neglect. Each color is associated to one disconnected link. The (dis)connectome is shown from sagittal view (right hemisphere), frontal view and superior view. The table further provides a β-weight per link. Parcellation into grey matter connectome nodes was done with respect to the Desikan-Killiany atlas (Desikan et al., 2006).

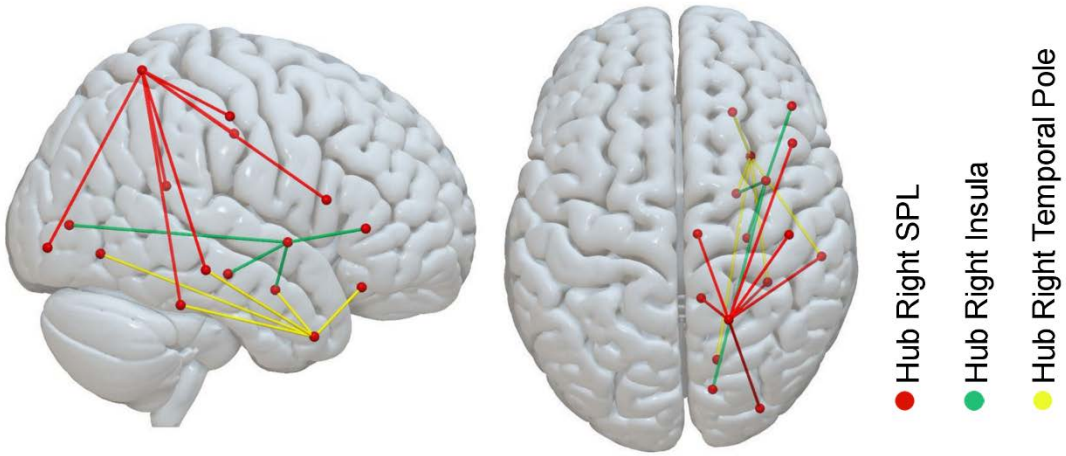


Figure 2: Results of the SVR-CLSM analysis reduced to crucial hubs

To better illustrate findings from Fig. 1, we segmented the (dis)connectome map into subnetworks, depending on whether there were continuous links between nodes or not. We extracted four different components. The figure shows disconnections of the three main hubs with continuously disconnected links of component one. Each color is associated to the disconnected edges of one of the three major hubs with more than three disconnections (the right insula, the right SPL and the right temporal pole). Results are shown from sagittal view (right hemisphere) and superior view. Parcellation into grey matter connectome nodes was done with respect to the Desikan-Killiany atlas (Desikan et al., 2006). Abbreviations: SPL – superior parietal lobule.

Discussion

The overall aim of the present investigation was to localise remote structural disconnection and central hubs in both hemispheres related to deficits of spatial neglect, following lesions in the right hemisphere. We combined a multivariate analysis technique based on support vector regression with connectome lesion-symptom mapping (SVR-CLSM) to predict the severity of spatial neglect. We detected three central nodes, namely the right superior parietal lobule, the right insula and the right temporal pole, which were extensively disconnected from other intrahemispheric areas. Moreover, central links to ventral prefrontal areas (i.e. inferior frontal gyrus and orbitofrontal cortex) and to the middle temporal gyrus were found within the network structure. Our results suggest that these areas might play a role within the anatomical network underlying spatial neglect.

Superior parietal lobule

Following an influential anatomo-functional model of visuospatial attention (Corbetta et al., 2008; Corbetta and Shulman, 2011), the superior parietal lobule and intraparietal sulcus (SPL/IPS) were considered to be part of a dorsal attention network (DAN) showing increased BOLD activity in controlled goal directed attention towards visual targets, reflecting endogenous attentional processing. In combination with the ventral attention network (VAN), reflecting exogeneous attentional capabilities, these two networks were assumed to contribute to normal visuospatial attention. Beyond, the authors suggested that disconnection of pathways of this network may play an important role in the development of spatial neglect (Corbetta et al., 2005; Corbetta and Shulman, 2011; He et al., 2007). In particular, they argued that structural damage to the VAN produces a functional alteration of the DAN - in the SPL/IPS - and that this structural-functional linkage is the main mechanism evoking the behavioural disorder.

In line with this model, our present SVR-CLSM analysis revealed the SPL as one of the three major hubs in which disconnection correlated with neglect severity. The analysis detected a disruption between the SPL and the inferior frontal gyrus (pars opercularis) in the ventral prefrontal cortex (VFC). The evaluation of functional imaging findings from He et al. (2007) in patients and healthy subjects together with findings of lesion-symptom mapping studies in neglect patients (Committeri et al., 2007; Toba et al., 2018, 2017; Verdon et al., 2010), lead to the suggestion that areas within the VFC − i.e. mainly the inferior and middle frontal gyri − might serve as critical coordination nodes between brain systems for endogenous (DAN) and exogeneous (VAN) spatial attention (Hattori et al., 2018). Following Hattori et al. (2018), projections of the inferior-frontal occipital fasciculus (IFOF) link superior parietal areas of the DAN (e.g. SPL, IPS) with areas of the VFC (see also Martino et al., 2010; Sarubbo et al., 2013). Accordingly, lesion studies showed that direct damage to the IFOF can lead to the development of spatial neglect (Karnath et al., 2011; Toba et al., 2018; Urbanski et al., 2008; Wiesen et al., 2019). Our present results might indicate that communication between DAN and VAN in spatial neglect patients is not only altered after damage to projections of the second branch of the superior longitudinal fasciculus (SLF II), as shown previously (Thiebaut de Schotten et al., 2014, 2005; Vaessen et al., 2016), but also by projections of the IFOF (i.e. disconnecting superior parietal and ventral frontal areas).

Albeit these considerable findings, the functional model of visuospatial attention as a comprehensive explanation for the development of spatial neglect was also criticised. The remote functional alteration of the SPL (evoked by a strucutral lesion of the VAN), leading to an interhemispheric imbalance between right and left SPL, i.e. left and right DAN function (Corbetta et al., 2005; Corbetta and Shulman, 2011) was also observed in further neurological samples. For example, Umarova et al. (2011) showed that an abnormal interhemispheric imbalance pattern between right and left parietal areas occurs independently of a positive neglect diagnosis after right hemispheric stroke and after using a similar 'spatial attention' paradigm as in Corbetta et al. (2005). Moreover, de Haan et al. (2013) evaluated the BOLD signal in acute stroke patients without neglect and observed an abnormal interhemispheric balance consisting of reduced signal change in perilesional areas of the damaged hemisphere relative to homologous areas in neurologically healthy controls, unrelated to the patients' behaviour. The data suggested that abnormal interhemispheric imbalance after stroke – such as the one reported by Corbetta et al. (2005) – could not only reflect functional disruption of these regions, but also a decoupling of the neurovascular response without changes in neuronal functioning and/or in the individuals' behaviour, or a combination of these two effects. Taking these findings together, the abnormal interhemispheric imbalance in the SPL/IPS region after damage in the VAN system might reflect a physiological epiphenomenon, for example, cerebrovascular reactivity (Barreto et al., 2011; D'Esposito et al., 2003; see for discussion Karnath, 2015; Martin et al., 2001), and not necessarily a change in neural function related to the behavioural defects in spatial neglect.

Moreover, there is a noticeable discrepancy in findings between lesion studies in neglect patients and studies using fMRI to investigate spatial attention in unimpaired subjects (as noted by Szczepanski et al., 2010). Structural lesion studies in stroke patient samples typically provide sparse evidence for a distinct role of the SPL in spatial neglect. To date, there are only few reports in patient studies devoting a role to the SPL/IPS complex in the occurrence of spatial neglect (Carter et al., 2017; Gillebert et al., 2011; Ten Brink et al., 2019; Toba et al., 2017; Vallar et al., 2014). Vice versa, it was reported that patients with lesions affecting SPL/IPS in particular, show attentional disorders but no spatial neglect. For example, Gillebert et al. (2011) demonstrated in two patients with small focal lesions (one with right SPL/IPS damage, the other with left IPS damage; in both cases the inferior parietal lobule was spared) that damage of

the SPL or IPS led to lateralised deficits in a spatial attention paradigm which were similar to those observed in a control group of patients with focal IPL damage. Specifically, these patients were not able to reorient their attention to and to select between competing stimuli for contralesional targets. Accordingly, Vandenberghe et al. (2012) noted that damage to the SPL or the IPS might generate a general spatial attention bias, occurring after right or left hemisphere damage. However, like Gillebert et al. (2011), they also noted that none of the patients with isolated SPL damage they discussed had clear signs of spatial neglect. These observations suggest that behavioural deficits observed after SPL/IPS damage are not spatial neglect specific. Rather, it appears that spatial neglect – at least the egocentric core symptoms as defined by Corbetta and Shulman (2011) and Karnath and Rorden (2012) – may be guided by mechanisms which are not strictly attentional.

On this background, Karnath (2015) has proposed that not the top-down control of spatial attention implemented in the DAN system appears to be disturbed in neglect patients but rather the matrix on top of which these voluntary shifts of spatial attention are executed. In fact, when neglect patients explore the surroundings by overt shifts of attention, they voluntarily execute movements into all possible directions without obvious direction-specific disturbances (Karnath et al., 1998; Niemeier and Karnath, 2000). The biased distribution of exploratory activity is assumed to result from an altered representation of own body position with respect to external objects. In neglect patients, this body-centred matrix (or egocentric reference frame of topographical information) is assumed to be rotated towards a new 'default position' on the right (cf. Karnath, 2015, 1994). In line with this view, studies showed that the biased exploration centre in neglect patients can be reweighted again to a normal 'position' by the systematic manipulation of afferent information, e.g., vestibular or neck-proprioceptive stimulation (Karnath et al., 1993; Rubens, 1985).

Insula

The second crucial hub in our analysis whose disruption to other brain regions contributed to the severity of spatial neglect, was the right insula. Lesion of this area was found to be related to spatial neglect in many previous lesion-behaviour mapping studies (Chechlacz et al., 2010a; Committeri et al., 2007; Golay et al., 2008; Karnath et al., 2011, 2004; Kenzie et al., 2015; Rengachary et al., 2011; Saj et al., 2012) and two ALE meta-analyses (Chechlacz et al., 2012; Molenberghs et al., 2012). In apparent

contradiction, Corbetta and Schulman (2011) suggested, that the insula as part of the VAN contributes mainly to non-spatial attention, for example, arousal and vigilance or the discrimination between relevant or novel stimuli. However, in addition to the spatial bias of exploration and attention, patients with spatial neglect also show many non-spatial attention deficits, which can further exaggerate the neglect-typical spatial biases (for example, Duhamel et al., 1992; Heide et al., 1995; Husain et al., 1997; Lamb and Robertson, 1988; Raymond et al., 1992; Robertson et al., 1997; Rueckert and Grafman, 1996). Together with the dorsolateral anterior cingulate cortex, the amygdala and other subcortical structures, the right insula is also often grouped as 'salience network' (for a discussion see Uddin et al., 2017). The damage to the link between right insula and amygdala observed in the present study could indicate that this 'salience network' is disturbed in patients with spatial neglect.

Temporal pole and the middle temporal gyrus

The temporal pole (TP) was identified as a third important hub in our analysis. It is an area of the brain rarely reported in lesion-behaviour mapping studies of spatial neglect. Specifically, TP lesions were described for one neglect patient (patient BD) in a study by Driver et al. (1994). In Wiesen et al. (2019), the TP directly contributed to the prediction of the severity of spatial neglect in the acute phase of the stroke. In a sample of 140 acute right brain damaged patients, Smith et al. (2013a) showed that power to predict spatial neglect was significantly increased when the TP was added to the pars triangularis of the inferior frontal gyrus and the supramarginal gyrus. Further, in a longitudinal study of 54 patients with right hemisphere damage, Karnath et al. (2011) found lesions of the TP to predict the persistence of spatial neglect symptoms in the chronic phase of the stroke. In line with these previous findings, our present analysis revealed that disconnections between the TP and parts of the orbitofrontal cortex contributes to neglect severity. The disconnection thus might reflect a disruption of the u-shaped uncinate fasciculus, connecting the TP to the VPC but also to the amygdala (Rojkova et al., 2016).

Interestingly, our results also depicted the right middle temporal gyrus (MTG) as disconnected to the SPL and TP in contributing to neglect severity. As shown in several previous lesion mapping studies, damage to the MTG seems to play an important role in spatial neglect (Chechlacz et al., 2010b; Committeri et al., 2007; Karnath et al., 2011, 2004; Rousseaux et al., 2015; Saj et al., 2012; Sarri et al., 2009;

Verdon et al., 2010; Wiesen et al., 2019). An important role of temporal structures in spatial neglect and covert attentional processing was also demonstrated in a recent investigation in the monkey brain (Bogadhi et al., 2019). This pioneering study showed how focal lesions affect whole attentional circuits in the brain and that pathological behaviour might not always be the consequence of damage to one exclusive brain node or connection. The authors temporarily inactivated an area at the intersection between the posterior middle and superior temporal gyri (posterior superior temporal sulcus [STS]) and observed spatial neglect-like symptoms in the monkeys' behaviour. They noted that this area in the temporal cortex might be a shared node between DAN and VAN. It is possible that the MTG node we identified in the present study actually relates to the STS. Unfortunately, we could not test this directly. In order to generate the healthy connectome in our analysis, we used pre-processed files of the IIT Human brain atlas using a gyral-based cortical parcellation (Desikan et al., 2006). Therefore, our analysis is restricted to this parcellation scheme, which does not account for the sulci in the brain.

Interhemispheric callosal connection

It was suggested that parietal interhemispheric callosal – especially splenial – disconnection might contribute to the development and persistence of spatial neglect (Bozzali et al., 2012; Lunven et al., 2015, 2014; Park et al., 2006; Pouget et al., 2011; Tomaiuolo et al., 2010). In contrast, our analysis revealed no disrupted links to left parietal brain areas as anatomical markers for spatial neglect. Rather, we observed that a link between left and right orbitofrontal cortices was disconnected and related to the disorder. The latter is in line with findings from Lunven et al. (2019), suggesting a role of frontal rather than parietal interhemispheric damage in spatial neglect and specifically a failure of rehabilitation by prism glasses.

Conclusion and perspective

Our findings underline the importance of a right hemispheric network structure in spatial exploration and attention with a few central hubs largely disconnected from other areas of the brain. The connectome lesion-symptom mapping approach combined with machine-learning based statistical analysis allowed us to point out a complex network structure in patients with spatial neglect. The present analysis and findings indicate that traditional lesion-behaviour mapping may be complemented by additional

analysis techniques, approaching step-by-step the high-dimensionality in lesion data. A remaining task for future studies is to analyse the specific contribution of each of these network nodes to the development of the behavioural disorder. Further, it is necessary to integrate these findings into current theoretical models about the pathophysiological mechanisms of spatial neglect as well as in models of normal processes of spatial exploration and attention.

Data and code availability statement

The datasets generated and analysed during the current study are not publicly available due to the data protection agreement of the Centre of Neurology at Tübingen University, as approved by the local ethics committee and signed by the participants. We provide the scripts of the main analyses, as well as the statistical topographies, available at http://dx.doi.org/10.17632/jgnpbpbbx5.1.

Acknowledgments

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Disconnection somewhere down the line: Multivariate lesion-symptom mapping of the line bisection error

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Disconnection somewhere down the line: Multivariate lesion-symptom mapping of the line bisection error

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Connectivity

ABSTRACT

Line Bisection is a simple task frequently used in stroke patients to diagnose disorders of spatial perception characterized by a directional bisection bias to the ipsilesional side. However, previous anatomical and behavioural findings are contradictory, and the diagnostic validity of the line bisection task has been challenged. We hereby aimed to re-analyse the anatomical basis of pathological line bisection by using multivariate lesion-symptom mapping and disconnection-symptom mapping based on support vector regression in a sample of 163 right hemispheric acute stroke patients. In line with some previous studies, we observed that pathological line bisection was related to more than a single focal lesion location. Cortical damage primarily to right parietal areas, particularly the inferior parietal lobe, including the angular gyrus, as well as damage to the right basal ganglia contributed to the pathology. In contrast to some previous studies, an involvement of frontal cortical brain areas in the line bisection task was not observed. Subcortically, damage to the right superior longitudinal fasciculus (I, II and III) and arcuate fasciculus as well as the internal capsule was associated with line bisection errors. Moreover, white matter damage of interhemispheric fibre bundles, such as the anterior commissure and posterior parts of the corpus callosum projecting into the left hemisphere, was predictive of pathological deviation in the line bisection task.

Abbreviations: VLSM, voxel-based lesion symptom mapping; FDR, false discovery rate; MLBM, Multivariate lesion behaviour mapping; SVR-LSM, SVR-based lesion-symptom mapping; SVR-DSM, SVR-based disconnection-symptom mapping; dTLVC, direct total lesion volume control; SLF, Superior Longitudinal Fasciculus; cTBS, continuous theta burst stimulation; LBE, Line Bisection Error.

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1. Introduction

The line bisection task is a widely used test in the diagnosis of spatial perception deficits after stroke. Originally, this task was introduced to assess visual field defects (for a review see Kerkhoff & Bucher, 2008) and later adopted in the diagnosis of spatial attention deficits (Schenkenberg et al., 1980), where it quickly became established as a routine test in neuropsychological test batteries (e.g., Halligan et al., 1991; Vaes et al., 2015). In the line bisection task, the patient is asked to manually mark the midpoint of a horizontally presented line. A deviation from the true midpoint to the ipsilesional side is typically seen as a sign of post-stroke deficits in spatial perception.

The neural correlates of line bisection errors (LBE) have been the subject of several studies that utilised either statistical lesion behaviour mapping (Kenzie et al., 2015; Molenberghs & Sale, 2011; Thiebaut de Schotten et al., 2014; Toba et al., 2018, 2017; Verdon et al., 2010) or descriptive topographical methods (Binder et al., 1992; Golay et al., 2008; Rorden et al., 2006). Most often, LBEs have been associated with damage to the posterior parietal lobe (Binder et al., 1992; Kenzie et al., 2015; Molenberghs & Sale, 2011; Rorden et al., 2006; Thiebaut de Schotten et al., 2014; Toba et al., 2017, 2018; Verdon et al., 2010). Other critical regions were found in the posterior part of the temporal lobe or the temporo-parietal junction (TPJ) (Kenzie et al., 2015; Rorden et al., 2006), frontal lobe (Thiebaut de Schotten et al., 2014), and parts of the occipital lobe (Binder et al., 1992; Kenzie et al., 2015; Rorden et al., 2006; Toba et al., 2018, 2017). Further, several studies have suggested a critical role of white matter damage (Golay et al., 2008; Thiebaut de Schotten et al., 2014; Toba et al., 2017, 2018; Verdon et al., 2010). The relevance of white matter tracts has also been highlighted by studies using either fibre tracking (Vaessen et al., 2016) or region of interest-based multivariate lesion analysis in left hemisphere stroke patients (Malherbe et al., 2018). Especially damage to the superior longitudinal fasciculus (SLF) (Malherbe et al., 2018; Thiebaut de Schotten et al., 2014; 2005; Toba et al., 2017, 2018; Vaessen et al., 2016) and the arcuate fasciculus (Malherbe et al., 2018; Thiebaut de Schotten et al., 2014) was found to underlie LBEs. Subcomponents of the SLF connect frontal areas, such as the middle frontal gyrus and pars opercularis, with parietal areas, such as the angular gyrus and the supramarginal gyrus (Thiebaut de Schotten et al., 2011a; Wang et al., 2016).

In conclusion, while there is considerable correspondence between findings in previous studies, it is not yet possible to find a unifying theory. A likely explanation for the different findings is that rather than damage to a single anatomical module, damage to a network underlies LBEs. The relevance of brain connectivity for most cognitive functions is well known (e.g., Godefroy et al., 1998; Catani & Ffytche, 2005) and has also been postulated to be relevant for spatial attention (Bartolomeo, 2006; Bartolomeo et al., 2007; Karnath, 2009; Karnath & Rorden, 2012). However, two exceptions aside (Malherbe et al., 2018; Toba et al., 2017), previous investigations used univariate topographical mapping approaches to investigate the neural correlates of line bisection. These come with methodological caveats in the identification of complex neural correlates of behavioural functions, especially with respect to brain networks (see Sperber, 2020; Sperber et al., 2019b). The two multivariate topographical studies both used an analysis approach based on game theory and included only a few brain regions of interest at once. Such a priori feature reduction by testing only a few possibly crucial hubs can be necessary due to computational or statistical limitations. However, the selected parcellation can differ from the relevant functional parcellation of the brain as well as the typical anatomy of stroke lesions. In contrast, voxel-wise analysis approaches are able to maximize an analysis' ability to identify neural correlates that are not expected, or that do not fully correspond to the brain parcellation provided by an anatomical atlas.

In order to integrate findings of previous investigations into a bigger, coherent picture, the present study thus aimed to identify possible networks underlying the line bisection task, using machine learning-based, multivariate voxel-wise analysis approaches. First, we used structural lesion data and conducted a multivariate lesion-behaviour mapping analysis to detect areas where focal damage might directly induce LBEs. This approach is powerful in identifying complex configurations of neural correlates such as in brain networks (Mah et al., 2014; Sperber et al., 2019b; Zhang et al., 2014). Second, by quantifying virtual white matter disconnection related to lesion location, i.e., depicting white matter connections in healthy brains running through patients' lesion areas, we further aimed to investigate remote pathological processes.

2. Methods

2.1. *Patient recruitment*

The sample consisted of 172 neurological patients admitted to the Centre of Neurology at Tuebingen University, which were screened for a first ever right-hemisphere stroke. The sample size was determined following recommendations from Sperber et al. (2019), concluding that sample sizes of at least 100–120 subjects are required to optimally model voxel-wise lesion location in SVR-LSM. We excluded patients with diffuse or bilateral brain lesions, patients with tumours, as well as patients in whom MRI or CT scans revealed no obvious lesions. As we were interested in the typical rightward LBE, we excluded nine patients with a leftward deviation in the line bisection task of more than 7.91% from the midline (see below), leaving 163 patients that were included in the present analyses. Table 1 shows demographic and clinical data of all 163 patients. 155 of these patients with valid line bisection testing were included in a previous study addressing the anatomy of spatial neglect evaluated with cancellation tasks (Wiesen et al., 2019). We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. Subjects gave their informed consent to participate in the study. The study was conducted in accordance with the ethical guidelines of the revised Declaration of Helsinki.

Table 1 – Demographic and clinical data of all 163 patients. For descriptive information it was determined whether a Line Bisection score was in the pathological range; the cut-off was an ipsilesional deviation of >7.77% (Sperber & Karnath, 2016a). Data are represented either i) as mean, with standard deviation in parentheses and range in brackets, or ii) as percent of the sample. Line bisection is reported as percent of deviation from the true midpoint.To determine if Centre of Cancellation (CoC) scores were in the pathological range, cut-offs were set at >.081 for the Bells Cancellation Task and >.083 for the Letter Cancellation test (Rorden & Karnath, 2010). Further we determined if patients with and without pathological scores differed significantly from each other (Mann-Whitney-U for continuous variables or Chi-Square for categorical variables).

	Bisection Bias	No Bias	X^2/U	sig.
Age (years)	60.4 (14.0) [18–81]	61.6 (13.8) [26–93]	2774	
Sex (M/F)	19/26	50/68	0	
Aetiology (Ischemia/Haemorrhage)	38/7	101/17	.034	
Lesion size (cm^3)	80.7 (66.9) [2.9–274.8]	28.5 (31.4) [.2–144.9]	1116	*
Time between lesion and assessment (days)	4.4 (3.9) [0–22]	4.0 (3.3) [0–17]	2401	
Line Bisection Bias (deviation)	21.1 (18.0) [8–83.2]	1.2 (3.2) [−7.5–7.6]	0	*
Bells (% above Cutoff/CoC)	62.2/.31 (.32) [−.03–.94]	28.0/.09 (.18) [−.11–.87]	1426	*
Letter (% above Cutoff/CoC)	48.8/.26 (.30) [−.02–.89]	17.0/.08 (.20) [−.06–.96]	1247	*
Visual Field Defects (N present)	27	89	1.673	

* < .001.

2.2. Neuropsychological examination

All patients underwent a neuropsychological examination including the Line Bisection Task (Schenkenberg et al., 1980), Letter Cancellation Task (Weintraub & Mesulam, 1985) and Bells Cancellation Task (Gauthier et al., 1989). The two cancellation tasks were administered and evaluated as previously described (Wiesen et al., 2019) and Centre of Cancellation scores (Rorden & Karnath, 2010) were used for descriptive reports (see Table 1). The mean time between stroke-onset and neuropsychological examination was 4.13 days (SD = 3.43 days). Visual field defects were assessed by confrontation technique.

For the line bisection task, a series of 10 horizontally oriented lines was presented and patients were asked to mark the line's midpoint with a pencil. Each line was 24 cm long, .5 cm wide, and presented separately on a sheet of paper. In order to avoid a systematic bias towards the middle of the sheet, half of the lines were drawn from the left margin of the sheet and half of the lines from the right margin. A displacement to the right side from the midpoint was coded positive and a displacement to the left negative. Line bisection deviation was assessed by averaging the distance between the true midpoint of the lines and the position marked by the patient across all 10 trials. Finally, the LBE was calculated as the percentage of deviation in reference to the maximal possible deviation to the left or right (e.g., −12 cm = −100% maximal to the left; 12 cm = 100% maximal to the right). As we were only interested in the rightward, ipsilesional bias, we excluded nine patients with a pathological contralesional deviation. The cutoff we used for pathological deviation to the left has been determined empirically in 44 healthy controls in a previous investigation (<-7.91%; Sperber & Karnath, 2016a). The non-significant correlation between the LBE and the presence or absence of visual field defects (r = .043, n.s) further shows that the LBE is not amplified through visual field defects in the present sample.

2.3. Imaging and lesion mapping

Structural imaging was acquired either by MRI (n = 82) or CT (n = 81), performed on average 3.3 days (SD = 4.5 days) after stroke-onset. If both imaging modalities were available, MR scans were preferred over CT scans. Lesions in the individual MR or CT scans were manually marked on transversal slices of the individual scan using MRIcron (www.mccauslandcenter.sc.edu/mricro/mricron). Normalization of CT or MR scans was performed using Clinical Toolbox (Rorden et al., 2012) in SPM8 (www.fil.ion.ucl.ac.uk/spm), which provides age-specific templates in MNI space for both CT and MR scans. If available, MR scans were co-registered with a high resolution T1-weighted structural scan in the normalization process. Fig. S1 shows a descriptive lesion overlap plot of all 163 patients and Fig. 1A of all 163 patients after application of the minimum lesion affection criterion of ~5%.

For the SVR-LSM analysis, lesion maps were vectorised while applying direct total lesion volume control (dTLVC; see Zhang et al., 2014), which is required in SVR-LSM (Zhang et al., 2014). In the present sample, lesion volume and behaviour showed a significant correlation of .50 ($p < .001$). For further analysis, a matrix with rows representing each case and columns representing the lesion status of each individual voxel was created.

To investigate white matter disconnection, we calculated disconnection maps using the BCBtoolkit (http://toolkit.bcblab.com; Foulon et al., 2018). Each individual lesion mask was used to identify fibre tracks passing through the lesioned area in a set of diffusion weighted imaging datasets of 10 healthy controls (Rojkova et al., 2016), similar to an approach previously used by Kuceyeski et al. (2013). In short, the normalized lesions of each patient were registered to every controls' native space using affine and diffeomorphic deformations (Avants et al., 2011; Klein et al., 2009). Next, tractography in Trackvis (Wang et al., 2007) was carried out while using the lesion masks as seed. Individual tractographies were

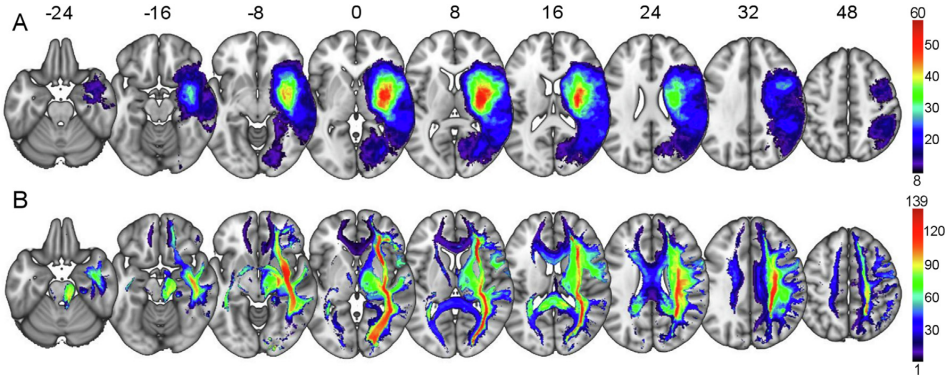

Fig. 1 – Topography of brain lesions and disconnections. A: Lesion overlap plot showing for each voxel the number of patients having a lesion at that location. Only voxels within the voxel mask for statistical testing with at least 8 (~5%) patients having a lesion are shown. The colourbar indicates the number of overlapping lesions (the peak of N = 60 represents 37% of the total sample). B: Lesion disconnection overlap plot of all 163 binarized disconnection probability maps, showing for each voxel the number of patients supposed to have a white matter disconnection at that location. A disconnection is assumed if the probability of disconnection surpasses 50% of being affected in the reference control sample. The colourbar indicates the number of overlapping disconnections (the peak of N = 139 represents 85% of the total sample). Numbers above slices indicate z-coordinates in MNI space. A lesion overlap plot of all patients can be found in the supplementary material (Fig. S1).

then used to create visitation maps, assigning at each voxel a value of 0 or 1 depending on whether the voxel fell into the streamlines of the tract (Thiebaut de Schotten et al., 2011a). These maps were further registered to the original normalized MNI space using the inverse of the precedent deformations. Finally, we calculated for each subject a percentage overlap map by summing at each voxel the normalized visitation map. The resulting disconnection map then indicates for each voxel a probability of disconnection from 0 to 100%, considering the interindividual variability of tract reconstructions in controls (Thiebaut de Schotten et al., 2015). For the subsequent statistical analysis, only voxels with a probability of disconnection of at least 50% were used as input features to predict the pathological behaviour. Fig. 1B shows a descriptive overlap plot of all binarized disconnection maps. We further provide overlap plots for the lesion maps and binarized disconnection maps based on scan modalities in the supplementary material (Fig. S2) showing no substantial differences related to MR or CT lesion delineation. Statistical testing (Mann-Whitney-U) further found no significant differences in lesion volume ($U = 2112.5$, n.s.) between lesions delineated by MR ($M = 43.89$, $SD = 45.69$) and lesions delineated by CT ($M = 42.16$, $SD = 53.82$).

The procedure for the estimation of the disconnection maps was based on the original lesions as masks for the tractography. It follows that the number of lesioned streamlines should be strongly related to lesion volumes of the seed masks, which can be confirmed in the present sample by the correlation between the number of affected voxels in the disconnection maps (hereafter labelled as 'disconnection size') and lesion volumes of the original lesion maps ($r = .83$; $p < .001$). Further the disconnection size is significantly related to the behavioural outcome ($r = .39$; $p < .001$). To account for this, each individual disconnection map was read into a vector including dTLVC (Direct total lesion volume control; see Zhang et al., 2014), which corrects for disconnection size in the same way as for the structural lesion map analysis above, ensuring comparability between the two analysis approaches. For the further analysis, a matrix with rows representing cases and columns representing the disconnection status of each individual voxel was used.

2.4. *Lesion analysis*

Our analyses were carried out with a multivariate method that has recently gained popularity in the field of lesion-symptom mapping, namely SVR-LSM (Support Vector Regression based Lesion Symptom Mapping). Support vector regression is a supervised machine learning technique (Cortes & Vapnik, 1995; Drucker et al., 1996) which is able to model the continuous relationship between lesion data and behavioural scores. This method has been employed and validated successfully in previous investigations with real lesion-symptom data (Fama et al., 2017; Griffis et al., 2017; Mirman et al., 2015; Wiesen et al., 2019; Zhang et al., 2014) and synthetic data (Sperber et al., 2019b; Zhang et al., 2014). For a detailed description of this method, we refer to the original study by Zhang et al. (2014). Using this same procedure, but with disconnection maps instead of traditional lesion maps, we additionally performed a disconnection-based multivariate analysis, named hereafter Support Vector Regression based Disconnection-Symptom Mapping (SVR-DSM).

All analyses were performed with MATLAB 2018b and libSVM 3.23 (Chang & Lin, 2013), using SVR with an RBF Kernel. We used a publicly available collection of scripts (https://github.com/yongsheng-zhang/SVR-LSM) employed in the original study by Zhang et al. (2014) and modified them to make effective use of our computational resources. Main

functions of the toolbox were not changed (see https://doi.org/10.17632/2hyhk44zrj.2 for public access to the modified analysis scripts). A complete guide on how to perform multivariate lesion-symptom mapping analyses based on support vector regression can be found in Karnath et al. (2019).

First, a parameter optimization procedure via grid search was carried out with lesion maps, as well as with the disconnection maps with 5-fold cross-validations to find the C and γ model parameters with the best trade-off between prediction accuracy and reproducibility, as in a previous investigation (Wiesen et al., 2019). This was done by employing a 5-times 5-fold cross-validation scheme, reflecting model quality when 4/5 of the dataset were used for building the model and 1/5 for testing it afterwards on an 'unknown' validation subset. Optimized model parameters C and γ were then used in the final SVR-LSM/SVR-DSM analyses.

The SVR β-parameters were derived for each voxel as described by Zhang et al. (2014), representing the strength of the association between each voxel's lesion or disconnection status and the behavioural score. These β-parameters were tested in a voxel-wise permutation algorithm to assess statistical significance by 10,000 permutations, controlled by False Discovery Rate (FDR; Benjamini & Yekutieli, 2001) correction at $q = .05$, and using a cluster threshold of 50 mm^3. For the analysis of structural lesion maps, significant results in cortical and subcortical grey matter regions were labelled with reference to the Automatic Anatomical Labelling atlas (AAL; Tzourio-Mazoyer et al., 2002) distributed with MRIcron (www.mccauslandcenter.sc.edu/mricro/mricron). Topographical results located in white matter were assessed using a tractography-based probabilistic fibre atlas (Thiebaut de Schotten et al., 2011b), extended by the SLF segmentations of a further probabilistic fibre atlas (Rojkova et al., 2016) and thresholded at $p \geq .3$ before being overlaid on the statistical topography of both the traditional lesion-symptom analysis and the lesion-symptom disconnection analysis. Note that the exact definition of some of these fibres and their subsegments – especially the SLF and arcuate fasciculus – differ across the literature. When interpreting our results, we followed the definitions provided by the above atlases.

Furthermore, only clusters with at least 50 mm^3 overlap with a labelled region are reported. Hence, there might be clusters larger than 50 mm^3 in size but without at least 50 mm^3 overlap with a labelled area, thus remaining unassigned.

3. Results

3.1. Parameter optimization

The parameter optimization routine for the structural lesion maps revealed an optimum $C = 10$ and $\gamma = 2$ which resulted in an average cross-validation prediction accuracy $r = .25$ and Reproducibility = .85. For the disconnection maps we achieved a similar model performance as for the lesion maps of prediction accuracy $r = .30$ and Reproducibility = .91, by using $C = 30$ and $\gamma = 9$.

Prediction accuracy appeared to be smaller than in previous publications using the technique (Sperber et al., 2019a; Wiesen et al., 2019; Zhang et al., 2014). However, it should be noted that, first, the prediction accuracy reflects prediction performance only after accounting for lesion volume, which is a required procedure for obtaining valid SVR-LSM results (DeMarco & Turkeltaub, 2018; Zhang et al., 2014). This also applies to the disconnection analysis, where larger lesions are more likely to increase disconnection rates. Second, cross-validation prediction accuracy is inherently limited in lesion-behaviour data based only on structural imaging (Sperber, 2020), and prediction accuracy values shown by the SVR-LSM/SVR-DSM technique are thought to only capture variance explainable by lesion-deficit relations, but do not consider further non-topographical variables that might explain additional variance.

3.2. SVR-LSM of lesion maps

The SVR-LSM analysis of structural lesion maps, FDR corrected at .05 and using lesion volume control by dTLVC, revealed only very few supra-threshold voxels (<20 connected voxels) and hence no interpretable pattern. The statistical topography can be found online (see data and code availability statement for open access to the files). FDR correction strongly depends on the overall signal in the data, and it might constitute an overly conservative correction method in situations with low signal (Karnath et al., 2018). As seen in the cross-validation, the SVR model's predictive power was indeed low, and considerably lower than in previous studies using the same methods and similar sample sizes (Sperber et al., 2019a; Wiesen et al., 2019). Accordingly, we post-hoc lowered the threshold to a still conservative cut-off of $p < .001$, uncorrected for multiple comparisons, but with a minimum cluster extent threshold of 50 mm^3 to further reduce the number of possible false positives. Thereafter, we found supra-threshold voxels in the inferior parietal lobule – especially within the angular gyrus – and a small cluster in the postcentral gyrus to be associated with LBEs. Moreover, a cluster in the pallidum and extending into the caudate nucleus was associated with LBEs. In white matter, voxels in the anterior commissure, the right arcuate fasciculus and the right superior longitudinal fasciculus (SLF II and SLF III) – SLF II intersecting the right angular gyrus – were associated with line bisection deviation. Note that the cluster overlapped with the arcuate fasciculus as delineated in its entirety by Thiebaut de Schotten et al. (2011b), but, following our procedures, we were unable to assign the cluster to one of the three subsegments of the fibre tract as delineated by the same study. An unassigned cluster larger than 50 mm^3 was detected at the white matter/grey matter border of the inferior temporal gyrus. For an exact overview on relevant clusters of voxels, including effect sizes (i.e., β-weights) and peaks, see Table 2 and Fig. 2.

3.3. SVR-DSM of disconnection maps

The SVR-DSM analysis of the disconnection maps (Fig. 2), FDR corrected at .05 with lesion volume control by dTLVC, showed disconnection to be significantly associated with LBEs in the right hemisphere within the internal capsule and all three branches of the superior longitudinal fasciculus (I, II and III). Moreover, fibres of the posterior corpus callosum and within

Table 2 – Significant grey and white matter clusters underlying the LBE in SVR-LSM. Labelling of significant right hemispheric grey and white matter areas found by SVR-LSM uncorrected at .001 after 10,000 permutations and a cluster extent threshold of 50 mm^3 before being overlaid on the corresponding atlas. Grey matter structures were identified with reference to the Automatic Anatomical Labelling atlas (AAL; Tzourio-Mazoyer et al., 2002). White matter structures were identified using a tractography-based probabilistic fibre atlas (Thiebaut de Schotten et al., 2011b), extended by the SLF segmentations of a further probabilistic fibre atlas (Rojkova et al., 2016) with regions of interest defined at a probability of $p \geq .3$. Only clusters with at least 50 mm^3 overlap with a corresponding atlas label are reported.

GM structure (AAL)	Number of voxels (mm^3)	β (Mean/SD)	β (Peak)
Angular gyrus	256	2.43/0.27	3.10
Pallidum	71	3.79/0.84	5.55
Inferior parietal lobe	63	2.89/0.28	3.55
Postcentral gyrus	56	2.81/0.21	3.40
WM structure (Thiebaut de Schotten et al., 2011b)	**Number of voxels (mm^3)**	**β (Mean/SD)**	**β (Peak)**
Arcuate fasciculus	154	2.47/0.26	3.19
Anterior commissure	57	3.19/0.98	5.09
WM structure (Rojkova et al., 2016)	**Number of voxels (mm^3)**	**β (Mean/SD)**	**β (Peak)**
Right SLF II	460	2.69/0.54	6.04
Right SLF III	389	2.70/0.57	5.87

the anterior commissure were implicated. A further large white matter cluster without corresponding atlas overlap was located close to the lateral part of the right inferior longitudinal fasciculus, between the inferior frontal gyrus and the middle temporal gyrus. For an exact overview on significant areas and effect sizes, see Table 3 and Fig. 2.

4. Discussion

The present study investigated the neural underpinnings of ipsilesional rightward line bisection deviation in acute right hemispheric stroke. We used both multivariate mapping of lesion maps to characterise direct structural damage as well as multivariate mapping of disconnection metrics to reveal additional remote effects of right-hemispheric lesions in both hemispheres.

4.1. *Grey matter damage related to the line bisection error*

By adapting the statistical threshold post-hoc to $p < .001$, uncorrected for multiple comparisons, several cortical nodes were found to be involved in line bisection deviation. This included primarily right parietal areas, particularly the inferior parietal lobe, including the angular gyrus, reflecting the importance of posterior brain structures that have been consistently reported by previous studies.

Using lesion overlap plots and subtraction analysis, Binder et al. (1992) described LBE as being associated with lesions in the posterior territory of the middle cerebral artery, incorporating the inferior parietal lobe with the angular and supramarginal gyri, as well as posterior parts of the middle temporal gyrus. Following a similar approach, Rorden et al. (2006) were able to replicate the initial findings from Binder et al. (1992) to some extent; they observed the critical area related to LBE at the junction between the middle occipital gyrus and middle temporal gyrus. Kaufman et al. (2009) used a multiperturbation analysis and reported that the top five areas playing a role for the line bisection task are the supramarginal and angular gyri, the superior parietal lobule, the thalamus and the anterior part of the temporo-parietal junction. Verdon et al. (2010) subsumed a battery of clinical tasks related to spatial attention into different components and found that line bisection mainly loaded on a factor that the authors attributed to perceptual abilities. An anatomical mapping of this component by VLSM implicated a location mainly around the inferior parietal lobe near the supramarginal gyrus. Molenberghs and Sale (2011) were able to replicate this finding by using VLSM and detected a significant cluster related to ipsilesional LBE at the medial part of the right angular gyrus. A slightly different pattern has been shown in the VLSM analysis by Thiebaut de Schotten et al. (2014), who adapted a liberal threshold of $p < .05$ uncorrected for multiple comparisons. The authors not only reported clusters in the superior parietal lobule, the supramarginal gyrus, temporo-parietal junction and the intraparietal sulcus between the angular gyrus and the superior parietal lobe, but also in the middle and inferior frontal gyri as well as the frontal eye fields and the precentral gyrus. Looking at the topographical maps (Thiebaut de Schotten et al., 2014, Fig. 2c), largest effects (i.e., highest z-scores) have nevertheless been detected within the inferior parietal lobule, precentral gyrus, angular and supramarginal gyri, and within the temporo-parietal junction. Interestingly, a pattern including frontal as well as parietal (angular gyrus and superior parietal lobe) and parieto-occipital regions, has been revealed already previously in a VLSM study by Vossel et al. (2011).

The involvement of frontal cortical brain areas in the line bisection task was not confirmed by the present investigation, although our advanced lesion mapping method should be especially suited to find multiple nodes of a network if present. So far only two investigations have reported a direct involvement of frontal cortical areas (Thiebaut de Schotten et al., 2014; Vossel et al., 2011). However, a considerable number of studies described an association of (mostly) caudal parts of fronto-parietal and fronto-occipital white matter pathways (e.g., inferior-longitudinal fasciculus, SLF, arcuate

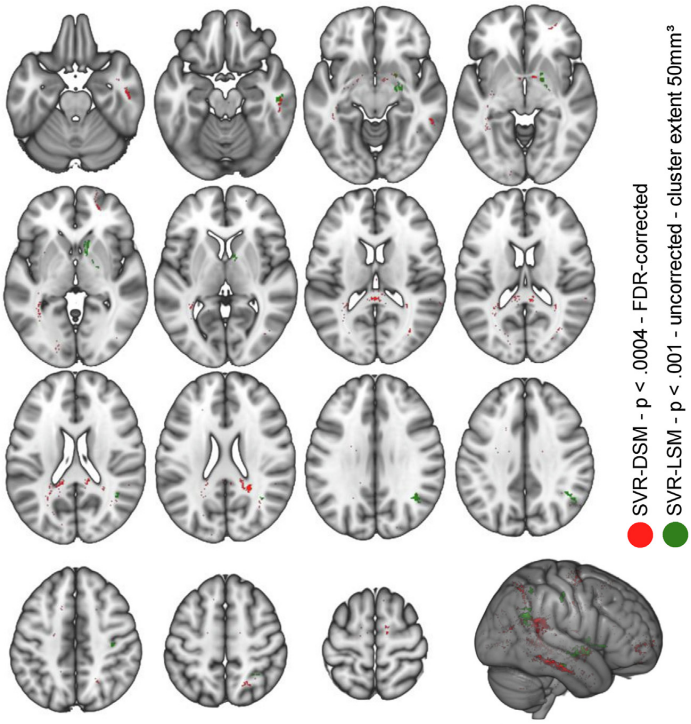

Fig. 2 – Results of the multivariate lesion-behaviour and disconnection-behaviour mapping. Support vector regression based multivariate lesion-symptom mapping and disconnection-symptom mapping results using data of 163 patients. Green: Permutation-thresholded statistical map of SVR-LSM on line bisection scores ($p < .001$, uncorrected for multiple comparisons), illustrating the anatomical regions significantly associated with the directional LBE. Red: Permutation-thresholded statistical map of SVR-DSM on line bisection scores ($p < .0004$, FDR-corrected at .05), illustrating virtual lesion-induced white matter disconnection significantly associated with the directional LBE.

fasciculus and inferior fronto-occipital fasciculus; see below). A possible explanation could be that frontal cortical areas were only rarely affected in some previous studies, and thus not included in the voxel-wise statistical analysis, especially in studies with a small number of cases. Instead, voxels eligible for inclusion into a voxel-wise analysis might have been located in frontal white matter areas, which are more often affected by stroke (cf. Sperber & Karnath, 2016b). Therefore, claims about the absence of frontal involvement in line bisection should be evaluated with caution, as such results might depend on sample characteristics. Accordingly, frontal cortical nodes were only sparsely tested in our analysis due to the exclusion of rarely affected voxels and were mainly restricted to posterior parts of the middle and inferior frontal gyri and the precentral gyrus (see Fig. 1A & Fig. S1).

A recently published multivariate study employing a game theoretical mapping approach showed that the intraparietal sulcus was the main contributor to rightward line bisection deviation (Toba et al., 2017). Additionally, synergistic influences between intraparietal sulcus, temporo-parietal junction and inferior occipital gyrus were reported as being crucial. In a further study, the same authors could delineate areas around the inferior parietal lobe, specifically the angular gyrus and occipital areas, as an anatomical basis of the LBE by VLSM (Toba et al., 2018). Their additional finding of occipital lobe involvement was not confirmed by our investigation.

Besides cortical grey matter influence, our analysis also implicated structural lesions subcortically in the right basal ganglia including the pallidum and extending into the caudate nucleus. The role of damage to the right basal ganglia in spatial attention might be linked to subcortical lesions inducing cortical malperfusion, and, thereby, leading to remote cortical dysfunction (Hillis et al., 2002; Karnath et al., 2005). However, a possible direct effect of subcortical lesions of the basal ganglia to the attentional bias has also been discussed (Parr & Friston, 2018). By simulating attentional deficits within a computational model and affecting the basal ganglia within the model structure, the authors demonstrated direct pathological consequences to the behavioural outcome.

Table 3 – Significant white matter clusters underlying the LBE in SVR-DSM. White matter areas where disconnection is associated with the LBE as found by disconnection based SVR-DSM, FDR corrected at .05 ($p < .0004$) based on 10,000 permutations. White matter structures were identified using a tractography-based probabilistic fibre atlas (Thiebaut de Schotten et al., 2011b), extended by the SLF segmentations of a further probabilistic fibre atlas (Rojkova et al., 2016) with regions of interest defined at a probability of $p \geq .3$. Only clusters with at least 50 mm^3 overlap with a corresponding atlas label are reported.

WM structure (Thiebaut de Schotten et al., 2011b)	Number of voxels (mm^3)	β (Mean/SD)	β (Peak)
Corpus Callosum	209	6.48/1.20	10
Anterior commissure	54	3.76/1.18	5.70
Right internal capsule	53	6.30/2.04	9.22
WM structure (Rojkova et al., 2016)	**Number of voxels (mm^3)**	**β (Mean/SD)**	**β (Peak)**
Right SLF I	311	4.59/1.65	9.05
Right SLF II	263	5.25/1.42	9.18
Right SLF III	88	3.00/2.12	9.18

4.2. *White matter disconnection related to the line bisection error*

Our lesion-symptom mapping analysis further showed involvement of the right superior longitudinal fasciculus (SLF II and III) and arcuate fasciculus, while the disconnection-symptom mapping analysis further delineated fibre disruptions within posterior parts (i.e., splenium) of the corpus callosum, and right internal capsule. Further, in the right hemisphere, all three branches of the SLF (SLF I, II & III) overlapped with significant areas of the disconnection topography. An additional non-assigned cluster was located close to the lateral part of the right inferior longitudinal fasciculus at the level of the right inferior temporal gyrus. Several clusters of voxels within the anterior commissure could be delineated by both lesion-symptom mapping and disconnection-symptom mapping.

Besides grey matter areas playing a role for the LBE, damage to white matter connections was reported previously (Golay et al., 2008; Malherbe et al., 2018; Thiebaut de Schotten et al., 2014; 2005; Toba et al., 2018; Vaessen et al., 2016; Verdon et al., 2010). Verdon et al. (2010) described an extension of the significant topography into white matter adjacent to the supramarginal gyrus. Thiebaut de Schotten et al. (2014) showed by track-wise hodological lesion-deficit analysis that the LBE is related to disconnection of the fronto-parietal segment of the arcuate fasciculus and of the second branch of the SLF (II).

When comparing the lesion topography of the VLSM analysis with a common white matter atlas (Thiebaut de Schotten et al., 2011b), Toba et al. (2018) reported involvement of the SLF III and the inferior fronto-occipital fasciculus. The authors also evaluated direct fibre tract involvement by using tractography and again found that SLF III integrity predicted rightward line bisection deviation. A descriptive evaluation of the lesion pattern showed that especially caudal disconnections of the SLF III lead to pathological performance. Our study confirmed the latter finding. Initial evidence of the involvement of the SLF comes also from a study using intraoperative electrical stimulation of the SLF and parietal areas during brain surgery (Thiebaut de Schotten et al., 2005). Notably the stimulation of the SLF resulted in greater LBE than stimulation of the right inferior parietal lobe or the posterior superior temporal gyrus, emphasizing again a crucial involvement of fronto-parietal connections in rightward line bisection deviation. With a multivariate approach, Malherbe et al. (2018) demonstrated synergetic effects between the SLF and superior temporal gyrus, as well as between the SLF and the inferior fronto-occipital fasciculus contributing to the explanation of leftward line bisection deviation. Vaessen et al. (2016) went further and looked directly at DTI-WM metrics. For a factor that loaded on line bisection and text reading, they mapped regions where reduced fractional anisotropy was linked to behavioural deficits. They found two significant clusters that were unaffected by macroscopic lesions, one located in the superior corona radiata adjacent to the trunk of the corpus callosum and the other in the splenium of the corpus callosum. They performed additional fibre tracking, using the clusters above as seeds. In patients scoring worse on this factor, this analysis showed lower track density in parts of the SLF II and III, as well as within the cortico-spinal tract, external capsule and callosal fibres projecting to the left inferior parietal lobe. Taking the second cluster as a seed, again the SLF at the level of the temporo-parietal junction and bilateral projections passing through the splenium of the corpus callosum were reported. Our disconnection analysis showed a similar pattern implicating callosal projection fibres running to the left hemisphere. Correspondingly, a recent intervention study using inhibitory continuous theta burst stimulation (cTBS) over the contralesional parietal lobe found integrity of posterior parts of the corpus callosum to be predictive for successful treatment of directional attentional biases (Nyffeler et al., 2019). Indeed, reduced callosal integrity has been found to be a predictor of persistent attentional deficits in the chronic stage (Lunven et al., 2015), as diagnosed amongst other tests with the line bisection task and leading to persistent symptoms even after therapeutic intervention by prism adaption (Lunven et al., 2019). There is evidence that left parietal areas show an increased BOLD response relative to homologue right hemispheric areas (Corbetta et al., 2005) in right hemisphere stroke patients with attentional deficits. Nyffeler et al. (2019) proposed that the pathological hyperexcitability can be normalised after left parietal cTBS and hence, might improve inter-hemispheric communication if callosal fibres are preserved. With respect to the findings of these authors, as well as Lunven et al. (2015, 2019), our results indicate that intact callosal fibres might not only be important for neglect recovery and therapy, but that callosal fibre

disconnection might also result in an exacerbation of the LBE to the ipsilesional side.

4.3. Relation of line bisection and cancellation tasks

It has been repeatedly reported that the directional bisection error dissociates from core symptoms of spatial neglect as measured by different cancellation tasks (Azouvi, 2002; Binder et al., 1992; Ferber & Karnath, 2001; McGlinchey-Berroth et al., 1996; McIntosh et al., 2017; Sperber & Karnath, 2016a; Toba et al., 2017; Verdon et al., 2010). These core symptoms include a spontaneous and sustained deviation of head and eyes to the ipsilesional side and ignoring stimuli on the contralesional side. A simple explanation for the behavioural dissociation between line bisection and cancellation tasks is an anatomical dissociation, i.e., both tasks at least partially rely on different anatomical correlates.

Several previous studies investigated and compared line bisection and cancellation within the same sample. The pioneering work of Binder et al. (1992) showed that patients with line bisection errors were likely to have posterior lesions, whereas patients who were impaired on the cancellation task had more anterior damage. This finding has been confirmed by Rorden et al. (2006), and also further studies found dissociations between both tasks (Thiebaut de Schotten et al., 2014; Vaessen et al., 2016; Verdon et al., 2010). Line bisection was associated with lesions to the inferior parietal lobe, posterior parts of the SLF, the arcuate fasciculus and nearby callosal fibres. In contrast, ipsilesional omissions in cancellation tasks were associated with lesions to middle and inferior frontal and superior temporal brain areas, frontal parts of parieto-frontal connections, and fronto-frontal connections (Thiebaut de Schotten et al., 2014; Vaessen et al., 2016; Verdon et al., 2010). On the other hand, Thiebaut de Schotten et al. (2014) also pointed at consistencies between the anatomy underlying deficits in both tasks. They observed disconnection of fibre tracks to lead to pathological behaviour in both tasks, especially for disruptions of the fronto-parietal segment of the arcuate fasciculus and the SLF II, originating from the angular gyrus and terminating in the middle frontal gyrus (Thiebaut de Schotten et al., 2011a; Wang et al., 2016). In a small sample of 25 patients, Toba et al. (2017) delineated for both tasks the intra parietal sulcus as the main contributor of performance and observed synergetic relations between several temporal, parietal, and occipital areas. The same authors also reported differences between both tasks. Only cancellation tasks were additionally related to synergetic interactions between the temporo-parietal junction and inferior frontal gyrus. In a combined structural and diffusion tensor imaging study, Toba et al. (2018) reported a central role of the angular gyrus, the inferior parietal lobe, the third branch of the SLF (SLF III) and the inferior fronto-occipital fasciculus for both behavioural tasks, whereas damage to inferior and middle frontal gyri correlated only with cancellation behaviour. Finally, Malherbe et al. (2018) found the inferior parietal lobe being crucial not only in ipsilesional line deviation, but also in contralesional omissions on the bells cancellation task in a left hemispheric patient sample.

Whereas the present study analysed the anatomical contributions to pathological line bisection deviation, the focus in the study by Wiesen et al. (2019) was to detect the anatomical correlates of the typical bias of neglect patients in cancellation tasks. Most of the patients (N = 155) in the present work were identical to those who participated already in the study by Wiesen et al. (2019). They found a large cortico-subcortical network, incorporating superior and middle temporal areas, and nearby inferior parietal and occipital structures. Interestingly, results also included frontal cortical areas and adjacent white matter. Albeit the anatomy underlying LBEs appears to differ in general from the anatomy found for the cancellation bias by Wiesen et al. (2019), it is interesting to see that there is also some correspondence between the neural correlates of both deficits. When comparing the present results to the recently published multivariate topography of the neural correlates of spatial neglect (Wiesen et al., 2019), this was especially notable for the parietal involvement and the callosal damage. The latter might indicate that pathological line deviation and the spatial neglect syndrome as measured by cancellation behaviour share some pathophysiological key processes.

4.4. Are we measuring the wrong line bisection error?

An explanation for the dissociations between a deficit in line bisection and a deficit in cancellation tasks (Azouvi, 2002; Binder et al., 1992; Ferber & Karnath, 2001; McGlinchey-Berroth et al., 1996; McIntosh et al., 2017; Sperber & Karnath, 2016a; Toba et al., 2017; Thiebaut de Schotten et al., 2014; Vaessen et al., 2016; Verdon et al., 2010) might be the lacking internal validity of the traditional way to administer and score line bisection task. LBEs are traditionally analysed, as in the present study, by measuring the deviation of the mark from the true midpoint. Recent studies challenged this traditional approach and instead proposed an alternative theoretical framework to administer and analyse line bisection (McIntosh et al., 2005; 2017). Within this framework, the locations of the left and right end points of the line and the bisection mark are coded in egocentric positions. Line bisection performance is then measured by assessing the influence of each individual end point location on the position of the mark. This results in two factors, of which one, contrary to traditional line bisection, indeed assesses the core symptom of spatial neglect (McIntosh et al., 2017), as measured also by cancellation tasks. Thus, the traditional line bisection assessment provides a biased and somewhat noisy measure of spatial neglect, which is additionally affected by a second factor potentially related to general attentional capabilities (McIntosh et al., 2017). This partial overlap of deficient cognitive functions in classical line bisection might explain divergent behavioural and anatomical findings in previous studies. Following this theoretical framework, line bisection is a noisy measure of spatial neglect, which explains the surprisingly weak prediction performance found in the present data. According to this interpretation, the mixture of at least two different cognitive functions might hamper the lesion-mapping algorithm to detect the true anatomical key areas related to the directional

line bisection deficit. Therefore, it will be crucial to use these new insights of McIntosh et al. (2017) into the line bisection task to derive new study protocols focusing systematically on the anatomical dissociations between these two factors.

4.5. *Heterogeneity in the anatomical correlates of line bisection errors*

Besides methodological differences in the investigation of the line bisection task as a result of using univariate versus multivariate approaches (see introduction section), further factors might have led to differences between the present and previous results, including factors such as line length, line position, or exact task demands (e.g., Cavézian et al., 2012; Doricchi et al., 2005; McIntosh et al., 2005). While it is difficult to explain all these findings from the classical theoretical perspectives on line bisection, the two-component theory of line bisection might do so (McIntosh et al., 2005; 2017). Notably, these different factors likely also underlie some of the variance of anatomical findings in the field. The presentation style of the line bisection task in the present study (ten lines of 24 cm length; five oriented along the right margin of the sheet, five oriented along the left margin of the sheet) likely affected the outcome to some degree, and might have led to differences between the present results and results in previous studies.

Another reason for heterogeneous results on the anatomy of line bisection errors in different studies might be the enigmatic role of visual field defects. A small LBE with a shift of the mark towards the contralesional side – mirroring the LBE typically attributed to deficits in spatial attention – is known to be related to visual field defects alone (Kerkhoff & Bucher, 2008). However, this effect was not found in acute stroke patients (Machner et al., 2009; Sperber & Karnath, 2016a), but instead visual field defects were found to be associated with higher LBEs in acute stroke (Daini et al., 2002; Doricchi & Angelelli, 1999; Doricchi et al., 2002; Sperber & Karnath, 2016a). This effect has been termed an 'amplification effect' of visual field defects, while, in fact, no generally accepted theory about the causal relation between both variables currently exists. A simple effect of lesion size, i.e., that larger lesions are both more likely to affect primary vision and more likely to induce high LBEs, is also imaginable. The more pronounced LBE in patients with visual field defects could explain why some studies found damage to more posterior brain regions to underlie LBEs compared to spatial neglect. Patients with primary visual defects typically have damage to posterior brain areas, and at the same time, they suffer from a more severe LBE due to the putative amplification effect. Thus, the statistical anatomo-behavioural signal might be enhanced in these posterior areas.

A further possible candidate to complicate the behavioural measure of LBEs could be contralesional deviation, which is sometimes called 'ipsilesional neglect' (Kim et al., 1999; Kwon & Heilman, 1991; Sacchetti et al., 2015; Sperber & Karnath, 2016a). Several studies implicated frontal brain areas for this behavioural finding (Kim et al., 1999; Sacchetti et al., 2015). Contralesional deviation is rather rare compared to the common LBE (Sperber & Karnath, 2016a). In the present study, we excluded cases with pathological contralesional deviation, but it is not known how both behavioural deficits are related and if it is the same cognitive processes that are symmetrically disrupted in both cases. It is unknown if both types of LBEs can interact, and if so, in what way they interact.

5. Conclusion and perspective

Our findings underline the importance of a network including several cortical nodes and intra-as well as interhemispheric connections in the emergence of the line bisection error. The use of support vector regression based lesion-symptom disconnection mapping revealed that we might miss relevant structures and connections when we only focus on focal damage. However, according to recent findings by McIntosh et al. (2017), the traditional interpretation of the line bisection task might produce a noisy measure, hindering the statistical algorithms to detect all of the relevant anatomical modules and connections. To resolve further inconsistencies in the literature, future studies should perform lesion-symptom mapping by disentangling spatial and non-spatial attentional components of the line bisection task as pointed out by McIntosh et al. (2017), in order to compare their neural correlates to those resulting from anatomo-behavioural analyses of similar tasks, such as cancellation tasks.

Data and code availability statement

The datasets generated and analyzed during the current study are not publicly available due to the data protection agreement of the Centre of Neurology at Tübingen University, as approved by the local ethics committee and signed by the participants. We provide the scripts of the main analyses, as well as the statistical topographies and overlap maps, available at https://doi.org/10.17632/2hyhk44zrj.2.

CRediT authorship contribution statement

Daniel Wiesen: Conceptualization, Writing – original draft, Formal analysis, Methodology, Investigation. **Christoph Sperber**: Conceptualization, Writing – original draft, Methodology, Investigation. **Hans-Otto Karnath**: Conceptualization, Writing - review & editing.

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Pre-registration Statement

No part of the study procedures was pre-registered prior to the research being conducted. No part of the study analyses was pre-registered prior to the research being conducted.

Supplementary data

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Anatomical substrates of visual extinction: A multivariate lesion analysis study in acute stroke

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Abstract

Multi-target attention, i.e. the ability to attend and respond to multiple visual targets presented simultaneously across both visual fields, is essential for everyday real-world behaviour. Given the close link between the neuropsychological deficit of extinction and attentional limits in healthy subjects, investigating the anatomy that underlies extinction is uniquely capable of providing important insights concerning the anatomy critical for normal multi-target attention. Previous lesion analysis studies into the relationship between visual extinction severity and lesion location have, however, produced heterogeneous results. In the current study, we used a multivariate statistical lesion analysis approach to investigate the anatomical substrate of visual extinction in a large sample of 108 acute stroke patients. The use of acute stroke patient data and a multivariate lesion analysis approach allowed us to address the issues associated with previous statistical lesion analysis studies and so estimate the full extent of the functional area or network associated with visual extinction, unconfounded by effects of functional reorganisation or secondary effects of brain damage. Our results reiterate that the temporo-parietal junction (TPJ) is critically associated with extinction, and highlight the urgent need for further research to clarify the precise cognitive role of the TPJ in multi-target attention.

Key words

Selective attention; Support vector regression; VLSM; Temporo-parietal junction

Introduction

Multi-target attention, i.e. the ability to attend and respond to multiple visual targets presented simultaneously across both visual fields, is essential for everyday real-world behaviour such as navigating traffic scenes, engaging in team sports, or playing a videogame. The importance of this ability is demonstrated particularly impressively in neurological patients suffering from extinction, typically as a consequence of right-hemispheric brain damage (Becker & Karnath, 2007). These patients are able to report single unilateral visual targets in either visual field, but are unable to report the contralesional target in bilateral situations where an ipsilesional target is concurrently present (de Haan et al., 2012; Oppenheim, 1885). Extinction is most commonly seen as a consequence of biased competitive interactions between the ipsilesional and contralesional target stimuli, and an exaggeration of the difficulty that healthy subjects have while trying to attend and respond to multiple targets presented simultaneously (de Haan et al., 2012; Desimone & Duncan, 1995; Driver et al., 1997; Duncan, 1998; Duncan et al., 1997; Mattingley, 2002). Given this close link between extinction and attentional limits in healthy subjects, investigating the anatomy that underlies extinction is uniquely capable of providing important insights concerning the anatomy critical for normal multi-target attention.

Several lesion studies in acute stroke patients have implicated the temporo-parietal junction (TPJ) in visual extinction (Karnath et al., 2003; Ticini et al., 2010). However, these studies performed descriptive lesion/malperfusion subtraction analyses where the lesion/malperfusion overlap map of patient without extinction was subtracted from the lesion/malperfusion overlap map of patients with extinction. These analyses allow us to determine which areas of the brain are more frequently damaged/malperfused in patients with than in patients without extinction (Rorden & Karnath, 2004), but allow no statistical inference.

To address this limitation associated with subtraction analyses, other lesion studies *statistically* assessed the relationship between visual extinction severity and lesion location (Chechlacz, Rotshtein, et al., 2013; Chechlacz, Terry, et al., 2013; Hillis et al., 2006; Vossel et al., 2011). These statistical lesion analysis studies have, however, produced heterogeneous findings. In line with the findings from the descriptive lesion studies, a statistical lesion analysis study by Chechlacz and colleagues (2013, Analysis 1) found that visual extinction was associated with damage centring on the TPJ. Other results from statistical lesion analysis studies have, however, implicated the angular

gyrus (Chechlacz, Rotshtein, et al., 2013, Analysis 2 and 3; Vossel et al., 2011), the supramarginal gyrus, medial temporal gyrus, and medial frontal gyrus (Chechlacz, Terry, et al., 2013), or the inferior occipital gyrus (Hillis et al., 2006) in visual extinction. Part of this heterogeneity across studies concerning the area(s) of the brain implicated in visual extinction may be due to subtle differences in analysis approach between studies (e.g. which covariates to include in the statistical analysis). However, this heterogeneity in previous analysis results may also reflect two more fundamental issues in these studies: the use of non-acute patient data and univariate lesion analysis approaches.

The vast majority of previous statistical lesion analysis studies investigating the anatomy underlying visual extinction relied on non-acute patient data. The use of acute stroke patient data is considered to be ideal for the study of the functional architecture of the healthy brain (see also de Haan & Karnath, 2018), but unfortunately this data is not always easy to access. The use of non-acute stroke patient data, however, while more readily available, complicates our ability to draw conclusions concerning the functional architecture of the healthy brain: Firstly, the results may be confounded by effects of functional reorganisation of the brain in the course of normal recovery (de Haan & Karnath, 2018; Karnath & Rennig, 2016; Karnath & Rorden, 2012). When a lesion analysis is performed using non-acute stroke patient data, the parts of the brain damaged in patients who have fully or partially recovered from their initial deficit are erroneously assumed to be not, or less critically, associated with the cognitive function of interest. As a consequence, the lesion analysis will fail to fully identify all areas of the brain associated with this cognitive function of interest. Secondly, the statistical lesion analysis results may be confounded by the presence of secondary effects of brain damage (such as sulcal widening and ventricle enlargement), that complicate the precise determination of the location and extent of the lesion (Karnath & Rorden, 2012). To our knowledge, the only lesion study to date to statistically assess the relationship between visual extinction and lesion location in acute stroke patients was performed by Hillis and colleagues (2006). This study, however, did not assess brain damage on a voxel-by-voxel basis, but classified five Brodmann regions as either affected or not affected by the brain damage. As such, both the spatial resolution and the brain coverage of the statistical lesion analysis was limited.

Additionally, all lesion studies conducted so far to uncover the anatomical substrate of visual extinction used a univariate lesion analysis approach. Such

univariate lesion analysis approaches, however, have limitations. Firstly, in univariate lesion analysis approaches, each voxel is considered an independent contributor to behaviour. Brain functions are, however, not organised in single voxels, but instead in larger functional areas or networks (Pustina et al., 2018). Moreover, brain damage following a stroke rarely affects a single voxel, but instead usually affects multiple voxels in typical patterns of collateral brain damage (Sperber & Karnath, 2017). Secondly, univariate lesion analysis approaches are vulnerable to the so-called "partial injury problem" (Rorden et al., 2009; Sperber, Wiesen, & Karnath, 2019). This problem occurs when the behavioural deficit of interest is seen following non-overlapping damage to different parts of the same functional area or network in different patients. In this situation, a univariate lesion analysis approach would treat each of these different parts of the same functional area or network as the control for the other parts, and so underestimate the full extent of the functional area or network associated with the behavioural deficit of interest. Given these issues, it has been suggested that multivariate lesion analysis approaches, which simultaneously consider the contribution of multiple voxels to behaviour, may be more appropriate (Karnath et al., 2018; Pustina et al., 2018). Several simulation studies have shown that multivariate lesion analysis approaches are indeed superior to univariate lesion analysis approaches in detecting brain networks (Mah et al., 2014; Pustina et al., 2018; Zhang et al., 2014).

In the current study, we use a multivariate statistical lesion analysis approach to investigate the anatomical substrate of visual extinction in a large sample of 108 acute stroke patients. The use of acute stroke patient data, and the multivariate lesion analysis approach will allow us to address the issues associated with previous statistical lesion analysis studies.

Methods and Materials

Patients

All subsequently admitted neurological patients with an acute, first-ever right hemisphere unilateral stroke were screened at the Tübinger Center of Neurology for potential inclusion in the current study. Inclusion criteria were: no evidence of older infarcts, no diffuse, bilateral, or cerebellar lesions, and no evidence of other neurological or psychiatric disorders. The final sample included 108 patients (see Table 1 for demographic data). All patients were volunteers and gave their informed consent.

The study was performed in accordance with the ethical standards laid down in the revised Declaration of Helsinki.

Table 1: Clinical and demographic data of all patients, and for patients with at least one contralesional omission in the bilateral stimulus presentation versus patients without any omissions. All numbers are reported as mean (standard deviation; minimum; maximum), except visual field defects, for which the number of patients without field defects/ with quadrantanopia/ with hemianopia are reported, and sex.

	All (N = 108)	Patients with ≥1 contralesional omission (N = 42)	Patients without any contralesional omissions (N = 66)
Omissions in bilateral presentation (%)	25.3 (38.9; 0; 100)	65.0 (36.1; 10; 100)	0 (0;0;0)
Spatial neglect (CoC score)	0.13 (0.21; -0.04; 0.85)	0.23 (0.26; -0.04; 0.80)	0.07 (0.14; -0.04; 0.85)
Age (years)	59.6 (13.3; 27; 93)	58.8 (13.1; 27; 80)	60.2 (13.5; 30; 93)
Sex (F,M)	50/58	18/24	32/24
Time lesion to Scan (days)	2.2 (2.3; 0; 8)	2.7 (2.3; 0; 8)	1.9 (2.4; 0; 8)
Time lesion to Assessment (days)	2.9 (1.9; 0; 7)	2.7 (1.9; 0; 7)	3.1 (1.9; 0; 7)
Lesion size on normalised scan (cm^3)	39.8 (41.5; 0.5; 234.8)	62.4 (50.4, 1.4; 234.8)	25.4 (26.2; 0.5; 103.4)
Visual field defects (no/QA/HA)	100/3/5	38/1/3	62/2/2

Neuropsychological assessment

Patients were neuropsychologically assessed in the acute post-stroke stage 2.9 days (SD = 1.9; range 0-7 days) after stroke onset (see Table 1). Visual field defects were assessed with the clinical confrontation technique, where the patient was required to detect a movement of the examiner's left or right index finger, presented in the patient's left or right visual field. Each patient was presented with 6 movements in each visual field, 2 in the upper quadrant, 2 on the horizontal meridian and 2 in the lower quadrant.

Visual extinction was assessed with a variation of the clinical confrontation technique where the patient was required to detect a movement of the examiner's left and/or right index finger presented in the patient's left and right visual field. Each patient was presented with 10 unilateral left, 10 unilateral right and 10 bilateral movements. In the rare instance that a patient displayed a visual field defect, care was taken to present the movements in the intact part of the visual field: In patients with lower or upper left visual field quadrantanopia (n=3), movements were presented in the intact upper or lower visual field respectively. In patients with left visual field hemianopia (n=5), movements were presented in the near and/or far periphery of the intact ipsilesional visual field. To determine the severity of visual extinction, the percentage of bilateral trials in which the patient failed to detect the contralesional movement (in the presence of correct detection of at least 90% of the contralesional movements during unilateral stimulation) was obtained.

To be able to control for potential effects of unilateral attentional biases on performance in the visual extinction assessment (Sperber et al., in press), we additionally assessed the severity of spatial neglect by determining the average Center of Cancellation (CoC) score (Rorden & Karnath, 2010) in two cancellation tasks. Each cancellation task was administered as paper and pencil test on a 21.0cm x 29.7cm A4 sheet of paper, placed in landscape orientation on the patient's sagittal midline. Patients were instructed to manually cancel out certain target items that were presented in a larger array of items including both target and distractor items. In the bells cancellation task (Gauthier et al., 1989), 35 solid black objects in the shape of bells had to be found among other black solid distractor items. In the letter cancellation task (Weintraub & Mesulam, 1985), 60 letters 'A' had to be found among other letters. No time limit was set for completion. The cancellation performance was evaluated by calculating the Center of Cancellation (CoC), a continuous measure that assesses the egocentric core component of spatial neglect (Rorden & Karnath, 2010). The CoC scores of both tests

were averaged to obtain a single score. The score 0 indicates a symmetrical cancellation performance, scores above 0 indicate a neglect-typical right-ward shift, with the score 1 indicating maximal possible neglect.

Imaging and lesion mapping

Brain imaging was obtained in the acute post-stroke stage, on average 2.2 days (SD = 2.3; maximum 8 days) after stroke onset (see Table 1). Acute clinical imaging was obtained from all patients either by CT or MR. If adequate imaging of both imaging modalities was available, MR was preferred. Only scans that displayed clearly demarcated lesions were used. For patients with MR, diffusion weighted imaging was utilised in the hyperacute stage up to 48h after stroke onset, and T2 weighted fluid-attenuated inversion recovery imaging afterwards (de Haan & Karnath, 2018). Lesions were manually drawn on transversal slices of the clinical scan using MRIcron (https://www.nitrc.org/projects/mricron). Normalisation of individual lesion maps to a common space was performed by Clinical Toolbox (Rorden et al., 2012). This software contains age-specific normalisation templates both for CT and MR imaging. The lesioned area was controlled for in the normalisation on individual base either by cost-function masking or enantiomorphic normalisation. Lesion delineation and normalisation were performed by experienced researchers (BdH, CS, and DW) and verified by consensus with a neurologist with more than 20 years of expertise in lesion mapping (HOK). A topography of lesions can be seen in Figure 1.

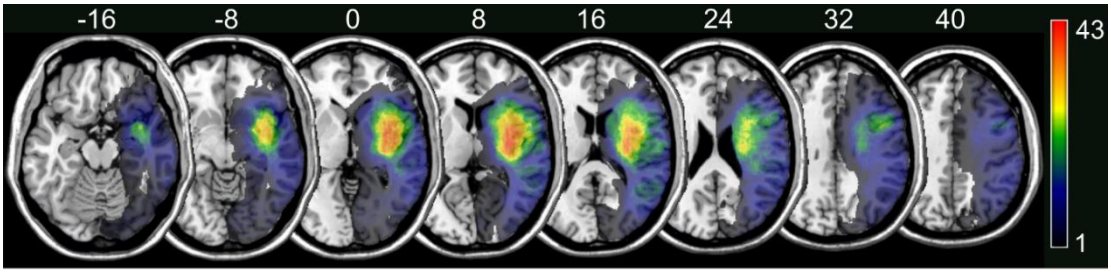

Figure 1: Lesion overlap map of all 108 lesions. Numbers above slices indicate z-coordinates in MNI-space.

Support vector regression-based lesion-symptom mapping

Lesion behaviour mapping was performed with support-vector regression-based lesion symptom mapping (SVR-LSM; DeMarco & Turkeltaub, 2018; Sperber, Wiesen, & Karnath, 2019; Zhang et al., 2014). This recently developed method is a multivariate approach to lesion behaviour mapping that, contrary to mass-univariate methods such as voxel-based lesion symptom mapping, models the lesion status of all voxels in the brain at once.

The method utilises support vector regression (Drucker et al., 1996), which is a machine learning-based multivariate regression approach. Using SVR, the damage status of all voxels that were affected in at least ten patients was used to model the behavioural outcome variable, i.e. the continuous extinction scores. Following the procedures in previous studies (DeMarco & Turkeltaub, 2018; Sperber, Wiesen, Goldenberg, et al., 2019; Sperber, Wiesen, & Karnath, 2019; Wiesen et al., 2019; Zhang et al., 2014), a non-linear ε-SVR with radial basis function kernel was chosen. A control for lesion size was implemented by direct total lesion volume control (Zhang et al., 2014). The extinction score, as obtained using the clinical confrontation technique, was controlled for potential effects of unilateral attentional biases on performance by regressing out the variance explained by spatial neglect, i.e. the average CoC score, from the behavioural score for extinction via nuisance regression. Hyperparameters C and γ were optimised for each individual analysis by a five-fold cross validation grid search. For this five-fold procedure, prediction accuracy and reproducibility of β-parameters was assessed (Zhang et al., 2014). To assess prediction accuracy, the SVR model taken from four fifths of the data was five times used to predict data in the last fifth of the data. Then, the average correlation out of all five runs was assessed. To assess reproducibility of β-parameters, the SVR model was five times computed for

four fifths of the data. Then, reproducibility was assessed by computing the average correlation of β-parameters between all these subsets. Following common procedures, we aimed to find hyperparameters that provided high reproducibility while still providing decent prediction accuracy (Rasmussen et al., 2012; Zhang et al., 2014). Considering that Zhang et al. (2014) performed a coarse grid searches that pointed at a smaller set of hyperparameters that can be considered, we only performed a fine grid search in the range of C = [1, 10, 20, 30, 40, 50, 60, 70, 80] and γ = [0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30]. Voxel-wise statistical inference was computed by testing the β-parameters obtained in the SVR by a permutation approach (Zhang et al., 2014) with 10000 permutations, and p-values were remapped into brain space. Further, a correction for multiple comparisons is required in SVR-LSM (Sperber, Wiesen, & Karnath, 2019), which was carried out by correction for false discovery rate (FDR) at q = 0.1. Statistical topographies were then interpreted by reference to brain atlases. Clusters of significant voxels in grey matter areas were identified using the maximum probability map of the Loni Probalistic Brain Atlas (Shattuck et al., 2008), and in white matter areas using maps of long association fibres in a probabilistic white matter atlas (Zhang et al., 2010). The probabilistic white matter maps were thresholded at $p \geq 0.4$ (for rationale see Eickhoff et al., 2005) to obtain a binary map for each fibre tract. All analyses were done using MATLAB 2018 and libSVM 3.21. The SVR-LSM analysis was performed using custom modified scripts based on the scripts by Yongsheng Zhang (Zhang et al., 2014; https://github.com/yongsheng-zhang/SVR-LSM).

Control analysis

To assess whether our method of controlling for potential effects of unilateral attentional biases on performance in the visual extinction assessment using nuisance regression was effective, we additionally assessed a subset of 39 patients without visual field defects (mean age = 56.7 years, SD = 11.2; 15 females, mean time between stroke and testing 3.4 days, SD = 2.1, range 0-7 days) on visual extinction using a computerised test with time-critical target presentation that allowed us to measure performance during both unilateral and bilateral trials, and calculate a so-called "extinction index" (Vossel et al., 2011). Each trial started with a central white fixation cross (0.6° x 0.6° visual angle) presented on a black background for a duration of 500ms. Patients were instructed to continuously fixate this fixation cross. This was followed by the presentation of a peripheral white target stimulus on the horizontal

midline at an eccentricity of 10.0° visual angle for a duration of 180ms. The target stimulus was a white geometrical shape (circle, square, triangle, or diamond; 1.5° x 1.5° visual angle), that was presented either unilaterally left, unilaterally right, or bilaterally. During bilateral presentations, the target stimuli were never identical. Patients were required to vocally report the location and shape of the target(s) presented (i.e. 'circle left' or 'diamond left and triangle right') while the experimenter logged these vocal responses on a sheet of paper. Finally, after the experimenter had made sure the patient was fixating the central fixation cross, the next trial was initiated by the experimenter with a keyboard response. In a single session, patients were presented with 10 unilateral left, 10 unilateral right and 10 bilateral targets in a pseudo-randomised order that was fixed over patients. We used the proportion correct (ranging from 0 to 1) during unilateral left and right target presentations, and bilateral target presentations to calculate an extinction index according to the following formula $I_{ext}=(P_{(hit\,|\,uni\text{-}left)}-P_{(hit\,|\,bil\text{-}left)})-(P_{(hit\,|\,uni\text{-}right)}-P_{(hit\,|\,bil\text{-}right)})$ (taken from Vossel et al., 2011). This extinction index ranges from 1 to -1 with a score of 1 reflecting complete contralateral extinction and a score of -1 reflecting complete ipsilateral extinction. Importantly, this extinction index provides a measure of extinction while controlling for unilateral attentional biases. Additionally, as in the main analysis, we used the percentage of bilateral trials in which the patient failed to detect the contralesional target to obtain an extinction score.

We used linear regression to regress the extinction score on the neglect score, i.e. the average CoC score. The residuals of this linear regression provide a measure of extinction that is controlled for the potential effects of unilateral attentional biases. Subsequently, we performed a Spearman's rank order correlation analysis to assess the correlation between the residuals of the linear regression and the extinction index. If our method of controlling for potential effects of unilateral attentional biases on performance in the visual extinction assessment using nuisance regression was effective, we would expect a strong and significant correlation between the residuals of this linear regression and the extinction index.

Results

Control analysis

In the computerised visual extinction task, on average 33% (SD = 38) of left stimuli in bilateral trials were omitted, and the extinction index was on average .25 (SD = .34). As expected, the results of our linear regression revealed that spatial neglect was a significant predictor of the extinction score (Beta = 1.199, $p < .0001$, $R^2 = .467$). More importantly, the Spearman's rank order correlation analysis revealed a strong and significant positive correlation between the residuals of the linear regression and the extinction index ($\rho = .737$, $p < .0001$). This suggests our method of controlling for potential effects of unilateral attentional biases on performance in the visual extinction assessment using nuisance regression was effective.

Support vector regression-based lesion-symptom mapping

The average size of the brain lesion in our stroke patients was 39.8cm³ (SD = 41.5). The average extinction score, as obtained using the clinical confrontation technique, was 25% (SD = 39). Forty-two out of the 108 patients omitted at least one left-sided stimulus in bilateral trials (see Table 1).

The grid search revealed the hyperparameters C = 40 and $\gamma = 2$ to be optimal with a prediction accuracy of $r = 0.38$ and a reproducibility of $r = 0.88$. The SVR-LSM identified 6700 suprathreshold voxels at an FDR of $q = 0.1$, equivalent to $p < 0.0057$ (Figure 2; Table 2). The majority of significant voxels was found in 3 larger clusters in inferior occipito-temporo-parietal regions in and around the TPJ. The largest cluster, abutting the inferoposterior end of the TPJ, included the middle occipital gyrus, angular gyrus, and posterior parts of the middle temporal gyrus. Two other larger clusters in the TPJ were found in the posterior superior temporal gyrus and inferior supramarginal gyrus. Significant voxels were nearly exclusively found in grey matter areas, except for a few voxels (approx. 5% of all suprathreshold voxels) reaching into parts of the superior longitudinal fasciculus.

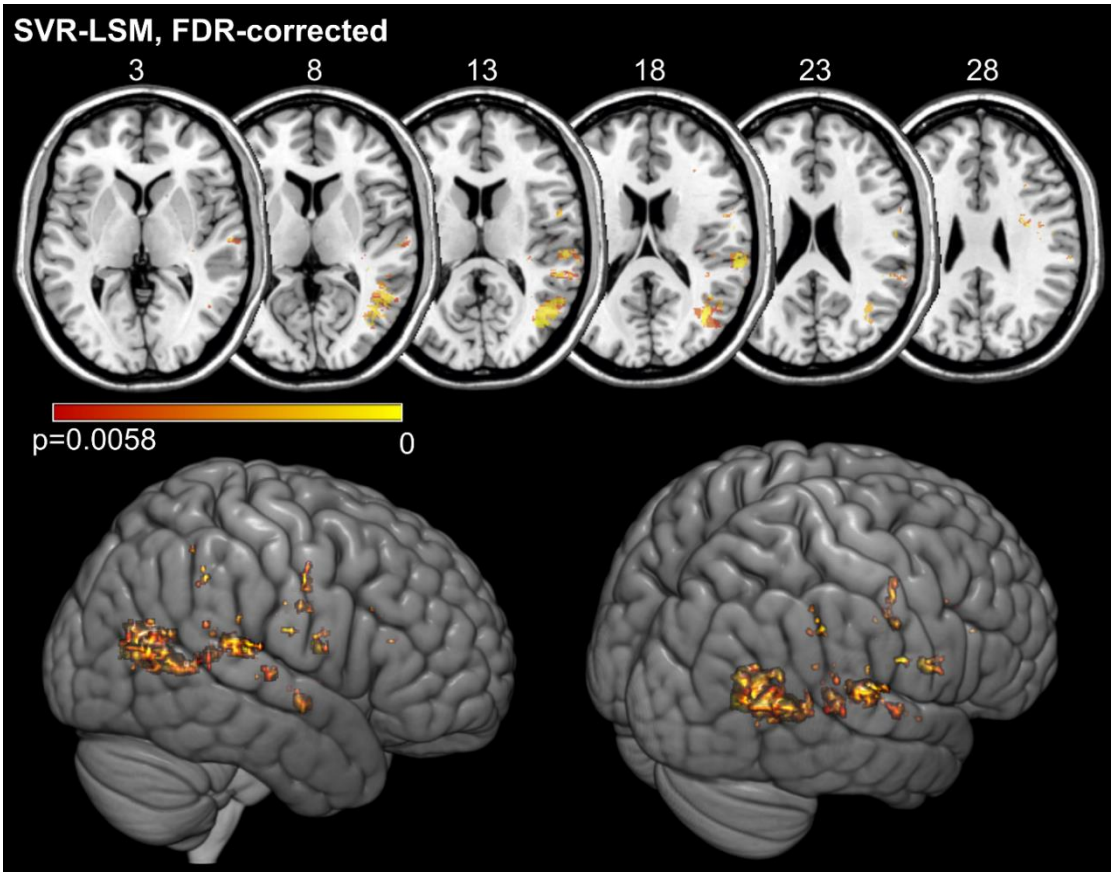

Figure 2: Neural substrates of visual extinction in acute stroke mapped by SVR-LSM. Extinction scores underlying the topography were controlled for spatial neglect. Permutation-thresholded voxel-wise results of SVR-LSM with a FDR correction at q = 0.1.

Table 2: Localisation of clusters of >100 significant voxels in the SVR-LSM analysis after FDR correction at q=0.05 as assigned by the Loni Probalistic Brain Atlas (Shattuck et al., 2008) and a probabilistic white matter atlas (Zhang et al., 2010) for long association fibres. Only regions with >15 voxels assigned to a cluster are reported. All numbers are in mm^3. SLF = superior longitudinal fasciculus.

Cluster number	1	2	3	4	5	6	7	8
Total cluster size	3963	781	329	196	181	180	173	114
Grey Matter Regions (Loni Probabilistic Brain Atlas)								
Middle occipital gyrus	2307	0	0	0	0	0	0	0
Middle temporal gyrus	1048	0	4	0	0	0	0	0
Superior temporal gyrus	7	524	315	196	0	0	0	0
Angular gyrus	572	0	10	0	0	0	0	73
Precentral gyrus	0	0	0	0	158	180	0	0
Supramarginal gyrus	0	257	0	0	0	0	0	41
Hippocampus	0	0	0	0	0	0	69	0
White Matter Regions (Probabilistic white matter atlas)								
SLF – parieto-temporal	284	0	0	0	0	0	0	0
SLF – fronto-parietal	0	0	0	0	0	83	0	0

Discussion

The current study examined the anatomy critical for normal multi-target attention by investigating the anatomy that underlies visual extinction. Prior lesion analysis studies have statistically investigated the relationship between visual extinction severity and lesion location (Chechlacz, Rotshtein, et al., 2013; Chechlacz, Terry, et al., 2013; Hillis et al., 2006; Vossel et al., 2011), but have produced heterogeneous findings. This heterogeneity of previous lesion analysis results may, at least in part, be due to two issues: Firstly, most of these previous studies relied on non-acute patient data. As a consequence, the results may have been confounded by effects of functional reorganisation of the brain in the course of normal recovery, as well as by the presence of secondary effects of brain damage. Secondly, all of these previous studies used a univariate lesion analysis approach. As a consequence, these analyses may have suffered from the "partial injury problem" and so underestimated the full extent of the

functional area or network associated with visual extinction. In the current study, we addressed both of these issues by using a multivariate statistical lesion analysis approach to investigate the anatomical substrate of visual extinction in a large sample of acute stroke patients.

Our results suggest that damage in a network of areas in and around the TPJ significantly predicts visual extinction severity. This result is in line with the results from descriptive lesion and malperfusion subtraction studies in acute patients (Karnath et al., 2003; Ticini et al., 2010), as well as the results of a univariate statistical lesion analysis study in non-acute patients by Chechlacz et al. (2013, Analysis 1). This result is also in line with the results from several studies in neurologically healthy participants that suggest a role for the TPJ in multi-target attention (Beume et al., 2015; Dugué et al., 2018; Meister et al., 2006). Of particular interest here is a recent study by Dugué et al. (2018), who identified three TPJ subregions that responded to bilateral visual stimulation whose location closely matches the location of the three clusters in and around the TPJ that we identified.

In this context, it is, however, puzzling that many other neuroimaging studies in healthy participants have failed to find evidence for a role of the TPJ in multi-target attention and its failure in extinction (Çiçek et al., 2007; de Haan et al., 2015; Geng et al., 2006; Gillebert et al., 2012; Praß & de Haan, 2019). Instead, these studies have tended to implicate the intraparietal sulcus (IPS). A key issue underlying these discrepant results, is that it remains unclear what precise cognitive role the TPJ plays in multi-target attention.

In single-target environments, the TPJ, as part of a right-lateralised ventral stimulus-driven attention network, has been associated with the stimulus-driven reorienting of attention towards unexpected behaviourally relevant stimuli presented outside of the current focus of attention (Corbetta et al., 2008; Corbetta & Shulman, 2002), or, more generally and domain-aspecific, with the stimulus-driven "contextual updating" of internal models of the behavioural context to allow the construction of appropriate expectations and responses following new sensory information (Geng & Vossel, 2013). Less, however, is known about role of TPJ in multi-target environments. The general, implicit assumption has been that the TPJ plays a very similar role in single- and multi-target environments (see discussion sections in Chechlacz, Rotshtein, et al., 2013; Karnath et al., 2003; Meister et al., 2006; Ticini et al., 2010). However, a study by de Haan and colleagues (2015) suggests that the part of the TPJ that

preferentially responds to unexpected over expected behaviourally relevant stimuli, shows no preference for bilateral over unilateral stimulus presentation conditions. Moreover, the view of the TPJ as an area associated with the detection of unexpected behaviourally relevant stimuli or contextual updating of internal models of the behavioural context does not fully explain how damage to the TPJ can selectively impair multi-target attention in the way seen in extinction patients.

A slightly different view posits that the TPJ is associated with the attentional selection / visual short-term memory (VSTM) encoding of new sensory input, particularly in multi-target situations. A highly influential model of selective attention views attentional selection as identical to VSTM encoding (Bundesen, 1990, 1998). As VSTM capacity is limited (Cowan, 2001), this may result in an interaction between VSTM maintenance and attentional selection / VSTM encoding in order to prevent the disruption of VSTM maintenance by new sensory information, particularly in multi-target situations where VSTM capacity limits have been reached. Studies have shown that whereas IPS activity increases with higher VSTM maintenance demands, TPJ activity decreases (Todd et al., 2005). Moreover, this decrease of TPJ activity during higher VSTM maintenance demands has been linked both to attentional selection / VSTM encoding deficits (Todd et al., 2005) that increase as a function of increased demands on attentional selection / VSTM encoding in multi-target environments (Emrich et al., 2011), and better VSTM maintenance task performance (Anticevic et al., 2010). Overall, this pattern suggests that TPJ deactivation during higher VSTM maintenance demands helps prevent the disruption of VSTM maintenance by new sensory information (Shulman et al., 2007; Todd et al., 2005). In this view, the TPJ is associated with the attentional selection / VSTM encoding of new sensory input, particularly in multi-target situations, a function that sometimes may have to be suppressed to support goal-directed behaviour.

One considerable problem with this explanation, however, is that overall, there is little support for the idea that activity in the TPJ increases as a function of increasing attentional selection / VSTM encoding demands. As mentioned above, apart from the single study by Beume et al. (2015), increasing attentional selection / VSTM encoding demands typically result not in an increase of activity in the TPJ, but instead in an increase of activity in the IPS (Çiçek et al., 2007; de Haan et al., 2015; Geng et al., 2006; Gillebert et al., 2012; Praß & de Haan, 2019). Indeed, some studies have suggested that the TPJ specifically responds to "target singletons" (Gillebert et al.,

2012), and transient disruption of the part of the TPJ deactivated during increased VSTM maintenance demands does not appear to modulate attentional selection / VSTM encoding (Praß & de Haan, 2019). This poses the puzzle that whereas TPJ *deactivation* (whether transiently, as a consequence of increased VSTM maintenance demands, or permanently, as a consequence of brain damage in extinction patients) impairs attentional selection / VSTM encoding, particularly in multi-target environments, TPJ *activation* does not seem reliably correlated with attentional selection / VSTM encoding demands. One possible solution to this puzzle is the proposal that the TPJ does not directly contribute to multi-target attention, but that functional damage to the TPJ simply results in remote dysfunction in the IPS (e.g. diaschisis-like effects, Feeney & Baron, 1986), similar to as what has been proposed for spatial neglect (Corbetta & Shulman, 2011). In this view, the IPS is associated with both VSTM maintenance and attentional selection / VSTM encoding, and the critical site for the interaction between VSTM maintenance and attentional selection / VSTM encoding in multi-target situations where VSTM capacity limits have been reached. This would fit well with the literature that implicates the IPS in both VSTM maintenance (Emrich et al., 2011; Mitchell & Cusack, 2008; Todd & Marois, 2004) and attentional selection / VSTM encoding (Çiçek et al., 2007; de Haan et al., 2015; Emrich et al., 2011; Geng et al., 2006; Gillebert et al., 2012; Mitchell & Cusack, 2008; Praß & de Haan, 2019). Moreover, there are suggestions in the literature that structural damage to the TPJ is associated with functional impairments in the IPS (He et al., 2007; Umarova et al., 2011). However, to the best of our knowledge, no study so far has been conducted to assess the relation between this remote dysfunction of the IPS following damage to the TPJ and multi-target attention. Indeed, the study by Umarova and colleagues (2011) suggests that this remote dysfunction at the IPS may represent a general consequence of right hemispheric brain damage independent of the presence or absence of attentional deficits.

Some researchers have instead suggested that the TPJ is associated with the integration of information across space and time (Davis et al., 2009; Hanayik et al., 2019; Husain & Rorden, 2003), as part of a "when" pathway located between the dorsal "where/how" and the ventral "what" pathways (Agosta et al., 2017; Battelli et al., 2007). The ability to integrate information across space and time is particularly crucial in multi-target environments where multiple objects temporally overlap. As such, it has been suggested that a failure of this ability critically underlies extinction (Hanayik et

al., 2019). Indeed, several studies have shown that extinction patients are impaired in temporal order judgment tasks (Baylis et al., 2002; Rorden et al., 1997). However, as these studies did not assess brain damaged patients without extinction, it is difficult to dissociate between general consequences of brain damage and deficits that are specific to extinction patients. Moreover, given that attention influences temporal perception (Hikosaka et al., 1993; Stelmach & Herdman, 1991), it is difficult to determine whether such deficits of temporal perception are the cause or a consequence of extinction. Other studies have found that patients with damage to the parietal lobe, and the TPJ in particular, are abnormally slow to process visual information (Duncan et al., 1999; Peers et al., 2005). These studies, however, did not assess whether these deficits were associated with extinction. The only study that did attempt to assess the link between impaired temporal processing and extinction (Habekost & Rostrup, 2006) only assessed patients with minor or no clinical signs of extinction. As such, their result that impaired temporal processing correlated moderately with extinction severity is difficult to interpret.

Taken together, our results reiterate that the TPJ is critically associated with multi-target attention and its failure in extinction patients. Over the years, various roles have been postulated for the TPJ, and these different views are far from mutually exclusive. Nevertheless, it is clear that further research is needed to clarify the precise role of the TPJ in multi-target attention and its failure in extinction patients.

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