THE NEUROANATOMY OF VISUOSPATIAL AWARENESS - LESSONS FROM LESION SYMPTOM MAPPING AND DIFFUSION TRACTOGRAPHY IN NEGLECT, EXTINCTION AND SIMULTANAGNOSIA

by

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ABSTRACT

The work presented in this thesis explored the structural and functional organization of visuospatial attention. This was done through advanced voxel-wise lesion symptom mapping methods used to decompose neuroanatomy of visuospatial disorders. The first study contrasted the neural substrates of different neglect symptoms, specifically the contributions of common and dissociable grey and white matter changes linked to allocentric and egocentric neglect. Two following studies decomposed the neuroanatomy of frequently co-occurring spatial attention syndromes by examining (1) the lesion patterns associated with visual and tactile extinction vs. those related to visual field defects and neglect, and (2) the lesion pattern linked to simultanagnosia, extracting out lesions associated with unilateral visuospatial deficits. These studies demonstrated that the different patterns of grey matter lesions in individual patients, and the laterality of white matter disconnections, determine the degree to which visual processing and spatial attention are disrupted and thus the nature of the observed cognitive symptoms.

The final study examined the neuroanatomy of subacute relative to chronic neglect and whether persistent neglect symptoms could be predicted based on clinical computed tomography scans acquired at stroke diagnosis. The findings provided evidence that although wide spread lesions are associated with acute symptoms, only some of these are critical for predicting whether neglect will become a chronic disorder. The pro's and con's of different approaches to lesion-symptom mapping are discussed, along with the theoretical implications for understanding the nature of human visual attention.

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CHAPTER 1:

METHODOLOGICAL BACKGROUND

"In any well-made machine one is ignorant of the working of most of the parts - the better they work the less we are conscious of them…it is only a fault which draws our attention to the existence of a mechanism at all."

(Kenneth Craik, The Nature of Explanation, 1943)

INTRODUCTION

Although the above citation from "The Nature of Explanation" (Craik, 1943) refers to the origins of Craik's concept of the "small-scale models" fundamental to modern cognitive science (and more specifically to mental model theories of thinking and reasoning; see for example (Johnson-Laird, 1983), somehow this quote is more universal and nicely captures the general concept behind cognitive neuropsychology and its methodological approaches including these employed in this thesis. Cognitive neuropsychology relies on data from individuals, who have compromised/impaired cognitive processes due to the specific patterns of neural damage, to shape and test theories of how the human brain works and is organized. In other words, cognitive neuropsychologists study the structural organization of the human brain and the mechanisms behind human brain function by focusing their attention on the faulty cognitive domains (symptoms) in neurological patients with different pattern of brain damage (lesions). This thesis will present four studies based on lesion-symptom mapping methods, which attempt to decompose the neuronal substrates underlying human visuospatial attention. Through these neuropsychological studies the aim is to learn about both the functional organization of human attention and its neuroanatomical substrates.

The research chapters (Chapters 2-5) presented in this thesis differ somewhat in terms of the specific features of the lesion-symptom mapping methods that were used, which were deliberately chosen based on the behavioural data available, the brain scans that had been

acquired and the characteristics of the patients who had been studied. Each research chapter is presented in the form of a self-contained manuscript including the relevant literature review, detailed description of specific methods used, and the justification of the methods and analyses as well as discussion and overall conclusions. Chapters 2-4 examine the relationship between visuospatial attention deficits and neuroanatomical change following acquired brain damage (mainly stroke but including heterogeneous neurological conditions) that are associated with the neuropsychological disorders of neglect, extinction and simultanagnosia. Chapter 5 focuses on the neuroanatomical difference underlying acute versus chronic visuospatial deficits following stroke recovery. In the present chapter I first review different neuroimaging modalities used to evaluate acquired brain damage in neurological patients, with particular emphasis on brain imaging methods applicable to stroke and to my research work. This is followed by a synopsis of the concepts and aims of cognitive neuropsychology. Finally, in the last part of this chapter I describe the principles and different approaches to lesion symptom mapping.

The closing chapter of my thesis (Chapter 6, General Discussion) provides a summary of the findings, overall conclusions and a critical evaluation of the applicability of lesion-symptom mapping techniques for understanding the structural and functional organization of visuospatial attention. The summary is followed by a short discussion of how research findings presented in this thesis fit with data from healthy controls including fMRI and TMS studies as well as studies using computational modelling (similar discussions are presented within empirical chapters). The rationale for this stems from my attempts throughout the thesis to put forward an argument that the selective application of various combined lesion-symptom mapping approaches has the potential to rejuvenate cognitive neuropsychology and to offer an elegant resolution to ongoing research debates between different groups, in this

case an ongoing dispute about the critical neural substrates of visuospatial attention (e.g., Mort et al., 2003 vs. Karnath, 2001; Karnath et al., 2001). The reviews focus primarily on stroke, since the great majority of patients who have entered into the present studies were stroke survivors.

NEUROIMAGING BRAIN DAMAGE FOLLOWING STROKE

Structural neuroimaging is used in medical practice to provide assessments of the extent of brain injury resulting from physical trauma (traumatic brain injury), stroke as well as from other causes including for example carbon monoxide poisoning (Coles, 2007; Gale et al., 1999; Guadagno et al., 2003; Hoggard et al., 2001; Hoggard et al., 2002; Horowitz et al., 1987; Mayer et al., 2000; Parkinson et al., 2002; Prockop and Naidu, 1999; Symms et al., 2004). The chief information provided by neuroimaging comes from estimates of the extent of structural damage, haemorrhage and ischemic changes following brain injury. This information is typically acquired in the acute phase to evaluate the necessity for surgical intervention, to plan treatment and to predict both immediate and long-term outcome. In the chronic stage following brain injury, structural neuroimaging findings can be applied to explain behavioural and neurocognitive problems, to evaluate recovery and/or to predict long-term outcome (Gallagher et al., 2007; Metting et al., 2007; Parkinson et al., 2002). The insights into mechanisms of cognitive dysfunction following brain injury that are provided by neuroimaging techniques are not only indispensable to medical practitioners but also to neuroscientists studying functional and structural organization of the human brain.

Brain injury leads to a variety of deficits affecting different cognitive domains depending on the location and the extent of the damage (for a recent review see Gottesman and Hillis, 2010). These cognitive deficits can include aphasia (language impairments),

neglect (spatial processing problems), apraxia (inability to perform purposeful skilled movements), visual perception, calculation and number processing problems, impaired executive function (i.e. decision making, problem solving), memory and learning (Engelter et al., 2006; Hajek et al., 1989; Paolucci et al., 1996; Ringman et al., 2004b; Tatemichi et al., 1994).

Structural imaging techniques such as computed tomography (CT) and standard magnetic resonance imaging (MRI; T1-weighted and T2-weighted scans) are currently used in medical practice to provide diagnosis and assessment of the extent of tissue damage after an injury. In addition, many of the past lesion-symptom mapping studies have used neuroimaging data based on standard MRI and CT scans. These techniques have different shortcomings, especially in the prognosis of outcome and are often insufficient to understand the neuroanatomy of cognitive deficits following brain injury. However, recent advances in neuroimaging have not only made it possible for clinicians to have a better understanding of the pathophysiology of damage associated with different neurological disorders, but they have also improved the planning of treatment and the understanding of recovery. Although the emerging imaging techniques are not widely used in medical practise, they have the potential to provide important insights into functional and cognitive recovery. For example, advances in structural imaging, particularly diffusion imaging such as diffusion weighted MRI (DWI) and diffusion tensor imaging (DTI), can significantly improve early and accurate detection of ischemic and infarcted tissue after stroke and allow clinicians to identify both brain tissue at risk of further damage and brain tissue with potential for recovery (Butcher et al., 2005; Fiebach et al., 2002; Gillard et al., 2001; Harris et al., 2008; Mukherjee et al., 2000; Redgrave et al., 2007; Schulz et al., 2003; Sotak, 2002). Thus it has been proposed that the assessment of white matter integrity based on DTI could be used as an index of stroke severity and the

likelihood of recovery and long-term disability (e.g. Gillard et al., 2001). It can also be argued that advances in both structural and functional neuroimaging can revolutionize our understanding of recovery after stroke and approaches to stroke treatment and rehabilitation (Baron et al., 2004; Boyd et al., 2007; Calautti and Baron, 2003; Guadagno et al., 2003; Munoz-Cespedes et al., 2005). These new brain imaging techniques have also reinvigorated modern cognitive neuropsychology. Below I discuss the advantages and limitations of different neuroimaging techniques, focusing on the assessment of both acute and chronic stroke, with an aim to provide a critical review how different methods including CT, standard anatomical MRI, perfusion and diffusion MRI are used in diagnosis. This is followed by an overview of the application of diffusion-based tractography and fMRI in the assessment of cognitive impairment and functional recovery after stroke. As these neuroimaging techniques have been also widely applied by cognitive neuropsychologists studying brain lesion data to infer structural and functional organization of the human brain, this approach to analysing brain function is also briefly reviewed. A more detailed overview of the application of neuroimaging data in lesion-symptom mapping is presented in the last part of this chapter.

Computed Tomography

Fast and reliable brain imaging is central to the diagnosis of stroke, to discriminate stroke from non-stroke, to differentiate ischemic (blood vessel blockage) from hemorrhagic stroke (bleed due to blood vessel rupture) and to select medical intervention (Wardlaw and Farrall, 2004; Wechsler, 2011). Computed tomography (CT) is an imaging modality based on X-rays that provides diagnostic tissue evaluation based on the degree of X-ray attenuation (Coles, 2007). Hemorrhagic stroke (bleed) is characterized by a high degree of X-ray attenuation and thus appears as hyperdense white area compared to the adjacent healthy brain

tissue (Kidwell and Wintermark, 2008). The early ischemic stroke is diagnosed based on hyperdense artery signs and/or loss of cortical grey-white matter differentiation (Krings et al., 2006; von Kummer et al., 2001). CT images acquired at a later stage following onset of ischemic stroke show areas of lower density that appear darker than adjacent healthy tissue due to reduced X-ray attenuation (Coles, 2007). In recent years many clinical trials have used either CT or MRI or both modalities as assessment tools for selecting courses of treatment i.e. to decide on therapy leading to the best possible functional outcomes (e.g. Albers et al., 2006; Chalela et al., 2007; Hacke et al., 2008; Kent et al., 2005; Wechsler, 2011). Some of these studies have raised questions about the sensitivity and future of CT scans in the evaluation of stroke (Kent et al., 2005; Chalela et al., 2007). CT imaging used to be and to a large degree still is the technique of choice for diagnosis of acute stroke. Despite the fact that in 1990's, novel techniques based on magnetic resonance imaging became widely available, CT remains more convenient and more accessible than any other modality, less expensive, more suitable for the majority of patients and finally both faster and superior for the detection of acute haemorrhage (Lovblad and Baird, 2010; Thijs, 2010; Wardlaw and Farrall, 2004). However the reliability of CT scanning for the diagnosis of sub-acute haemorrhage is somewhat limited and even more importantly CT often fails to precisely diagnose ischemic stroke, especially at early stages of diagnosis (Wardlaw and Farrall, 2004; Chalela et al., 2007). These shortcomings of CT imaging have important implications for both clinical practise and research in cognitive neuropsychology. Many stroke patients remain disabled despite treatment following early imaging finding and diagnosis based on CT scans, therefore the fundamental question is whether superior diagnostic abilities offered by other neuroimaging modalities will result in better functional outcomes of treatment (Wechsler, 2011). Some of the new techniques, based on MRI (see below) provide a solution to the well-known

phenomenon of "clinical CT mismatch" i.e. the mismatch between the severity of functional deficits and the extent of neuroimaging findings on CT scans (von Kummer et al., 2001; Kent et al., 2005). This is of particular significance from the point of view of the cognitive neuropsychologist who may use CT scans in brain function studies based on lesion-symptom mapping (e.g. Bird et al., 2006; Karnath et al., 2004; Karnath et al., 2003; see also Ticini et al., 2010). Notably, there is a “conflict of interest” between clinicians and researchers in terms of when is the optimal time to obtain a CT scan. The chief clinical value of CT is fast accurate detection of haemorrhage as soon as it has occurred and the clinical imperative is to scan patients as soon as possible, even a few hours after onset. However, such early scans are poor in detecting signs of ischemia. The ischemic stroke, which accounts for the larger proportion of all stroke cases does not show on CT scan until between 2 and 7 days after onset, depending on the stroke severity (Wardlaw and Farrall, 2004). Thus from the point of view of lesion-symptom mapping studies, the longer time lapse between the stroke onset and the CT scan is better. Taking into consideration all of the above points, some caution is necessary when considering the inclusion and exclusion criteria for cognitive neuropsychological studies in terms of the timing of acquiring CT data and the timing of cognitive testing. Subsequently, the limitations of CT imaging need to be taken into account when conclusions are drawn.

Magnetic Resonance Imaging

The main advantage of MRI compared to CT imaging in the diagnosis of stroke is the ability to correctly detect both acute haemorrhage and acute ischemia. Overall MRI has been proved to be a better diagnostic tool irrespective of the time of stroke onset (Chalela et al., 2007; Fiebach et al., 2004; Kidwell et al., 2004). Nevertheless, this technique is not widely

available, and remains relatively expensive as well as not suitable for all patients due to several common contraindications including presence of metallic bodies and pacemakers. As a result MRI is still less frequently used as compared to CT in medical practise (Chalela et al., 2007; Wardlaw and Farrall, 2004). MRI uses variations in the number of protons in the body to generate images on the basis of principles of nuclear magnetic resonance. Type of stroke, time since onset, the strength of the magnetic field and the type of sequence used determine the MRI signal characteristics of stroke (Kidwell and Wintermark, 2008; Kloska et al., 2010). For example, acute haemorrhage is hypointense on both standard T1-weighted and T2-weighted scans. In contrast acute ischemic infarct is hypointense and often difficult to see on a T1-weighted scan but is well defined and hyperintense on T2-weighted scans. Although, the two conventional MRI techniques, T1-weighted and T-2 weighted scans, provide useful diagnostic information and have certain advantages over CT, the superior rank of MRI in stroke evaluation has been established through newer techniques such as diffusion weighted (DWI) and perfusion weighted (PWI) imaging (Abe et al., 2003; Farr and Wegener, 2010; Kloska et al., 2010; Wechsler, 2011).

Both DWI and PWI have improved significantly the assessment of stroke outcome in terms of providing a better evaluation of tissue at risk i.e. detecting areas that are likely to undergo infarction. DWI is sensitive to random movement of water molecules within tissues and allows estimates of the shifts in this random motion (i.e. increased or restricted diffusion) resulting from tissue injury following stroke onset (e.g. Hossmann et al., 1994; Schaefer et al., 2000; Warach et al., 1992a). DWI provides a measure of water diffusion with respect to cellular structure and membrane permeability, which is expressed as the apparent diffusion coefficient (ADC). Following stroke onset, the ischemic changes in the brain tissue result in the ADC reduction and the ADC decrease is believed to be the most sensitive method for the

detection of early infarction (Fiebach et al., 2002; Mohr et al., 1995; Saur et al., 2003; Schaefer et al., 2000). However, not all areas of abnormality (i.e. the lesion) detected on DWI represent irreversibly damaged tissue and some areas recover without progressing to infarction (Fiehler et al., 2004; Kidwell et al., 2000). Thus, a simple approach based on DWI derived ADC value alone is not the best strategy for detecting the tissue at risk. This led to the development of the DWI/PWI mismatch model (see below; Butcher et al., 2005; Neumann-Haefelin et al., 1999; Oppenheim et al., 2001; Sims et al., 2009; Sorensen et al., 1996; Wu et al., 2001). Perfusion weighted imaging (PWI) provides a measure of capillary perfusion within the brain based on a paramagnetic contrast agent injected into the blood stream of the patient (Aksoy and Lev, 2000; Grandin, 2003; Rosen et al., 1990). The changes in tissue perfusion resulting from the occlusion of blood vessels have been shown to be a reliable predictor of poor functional outcome (Warach et al., 1996; Warach et al., 1992b). In particular, the severity of hypoperfusion is a key determinant of outcome and it has been demonstrated that brain areas with severely compromised perfusion are likely to progress to infarction (Butcher et al., 2003). However, restoration of blood flow that improves perfusion not only can salvage the tissue at risk of infarction but also improve cognitive functioning (e.g., Heiss et al., 1998; Hillis et al., 2006b). Thus the DWI/PWI mismatch concept was developed to further improve the evaluation of tissue at risk of infarction. The main principle of the mismatch model is based on the difference between the areas of abnormality detected by the two modalities. If the affected area identified by perfusion imaging is significantly larger than the area identified by diffusion imaging, the area of mismatch represents tissue at risk of infarction (also known as the ischemic penumbra) but still salvageable (Baird et al., 1997; Neumann-Haefelin et al., 1999; Wu et al., 2001). However, if the areas of perfusion and diffusion abnormalities are matching or if the perfusion abnormality is significantly smaller

than the DWI lesion, then the procedure will represent non-salvageable tissue (Sorensen et al., 1996; Baird et al., 1997). Finally, it should be noted that both DWI and PWI have been shown not only to reliably predict ischemic penumbra but also to correlate well with the severity of cognitive dysfunction (Hillis et al., 2002; Hillis et al., 2001; Shirani et al., 2009). In particular, perfusion imaging has been applied in several recent cognitive neuropsychological studies investigating the anatomy of different cognitive domains including spatial attention and aphasia (e.g. Hillis et al., 2000a; Hillis et al., 2005; Hillis et al., 2000b; Karnath et al., 2005; Ticini et al., 2010). These studies demonstrate the important principle that cognitive deficits might result not just from lesions that are well defined by structural imaging but also because of cortical dysfunction within a region that is structurally intact but has inadequate cortical perfusion.

Diffusion Tensor Imaging and Functional MRI

DTI and fMRI are two neuroimaging techniques, which although not routinely used in medical practice, have the potential to supply important insights into recovery after stroke. Functional MRI (fMRI) is a technique that provides an indirect measure of neuronal activity based on BOLD (Blood-Oxygenation-Level-Dependent) contrast sensitive to local differences in the magnetic field generated from changes in deoxygenated haemoglobin. The BOLD signal results from interactions between changes in blood flow, blood volume and oxygenation levels associated with neuronal activity and it measures metabolic (oxygen) demands of neurons and not activity per se (Kwong et al., 1992; Ogawa et al., 1993). As previously reviewed (see above) diffusion weighted imaging (DWI) is an MRI technique that utilizes the sensitivity of proton MRI signal to diffusion of water molecules and DWI-derived the apparent diffusion coefficient (ADC) provides a measure of water diffusion with respect

to cellular structure and membrane permeability. Thus, ADC is commonly used as a marker of ischemic changes in the brain tissue following stroke. However, based on the basic diffusion MRI (i.e. DWI) the highly anisotropic (directional) diffusion within white matter cannot be fully represented and quantified. Subsequently, Basser et al. (1994) introduced diffusion tensor imaging (DTI) as a way of completely describing the random and highly directional diffusivity of water molecules in vivo. Basser et al. (1994) proposed that based on acquisition of diffusion weighted data in at least six non-collinear directions, it would be possible to estimate the diffusion tensor (a 3x3 symmetric matrix) that fully characterizes anisotropic diffusion. As a result, diffusion tensor imaging is an MRI technique of choice that based on water diffusion allows estimations of the organization and structural integrity of white matter (Basser et al., 1994; Basser and Pierpaoli, 1996). The directionality of water diffusion (anisotropy) in the white matter within the brain depends on the alignment of neuronal axons and the main determinant of anisotropy is the presence of intact cell membranes (Beaulieu, 2002; Wiegell et al., 2000). DTI measures differences in the directionality of water molecules with respect to white matter fibre tracts and one of the DTI-derived measures often used as a predictor of functional recovery is fractional anisotropy (FA) i.e. the degree of directionality of water diffusion (Basser and Pierpaoli, 1996). Tractography is a technique allowing non-invasive reconstruction and visualization of white matter pathways based on diffusion data (Le Bihan et al., 2001; Mori and Zhang, 2006; Poupon et al., 2000). Although clinical applications of fMRI and DTI are still in development, their contributions to understanding cognitive dysfunction following stroke-associated tissue damage are undeniable. Therefore below I provide an overview of both modalities in the context of the evaluation of cognitive and behavioural problems following stroke (functional decline) as well as functional recovery.

DTI and DTI based tractography provide an opportunity to evaluate white matter pathology, to identify damage within specific neuronal pathways, to detect alterations in neuronal connectivity resulting from brain lesions and to evaluate any reorganization with neuronal networks (reflecting neuroplasticity following a lesion). For example using DTI Breier et al. (2008) demonstrated a relationship between deficits in the repetition of speech after stroke and damage within the superior longitudinal and arcuate fasciculi as assessed by decreased FA values. Interestingly, Stinear et al. (2007) demonstrated recovery of FA values within the internal capsule following 30 days of motor training, with FA values being associated with an individual patient's potential for functional recovery. Several different research groups have now provided evidence for a relationship between motor outcome after stroke and damage within the corticospinal tract based on correlations between the clinical symptoms and the findings from tractography showing changes in structural integrity (Cho et al., 2007; Kunimatsu et al., 2003; Lee et al., 2005; Moller et al., 2007; Yamada et al., 2004). Importantly, Pannek et al. (2009) correlated changes in connectivity estimations within the ischemic hemisphere (reflecting white matter reorganization) and recovery from stroke (see also Crofts et al., 2011; Johansen-Berg, 2007b).

Although, DTI tractography findings are remarkable, the future of its clinical applications needs careful evaluation. First, the sensitivity of tractography to detect stroke-associated changes within white matter pathways is highly dependent on the number of diffusion direction and the gradient strength used, as well as on often quite complex data analysis protocols. Therefore, current clinical use of tractography is not feasible. Second, it should be noted that existing algorithms for DTI tractography are highly susceptible to both false positives and false negatives. Thus its findings demonstrating either the presence or absence of white matter pathways following stroke might be a product of false reconstructions

in the presence of oedema or tissue damage and degeneration (Ciccarelli et al., 2008; Pierpaoli et al., 2001; Sotak, 2002). The final point here is that DTI tractography revolutionized modern cognitive neuropsychology by triggering the renaissance of Geschwind's concept of a disconnection syndrome (Catani and Ffytche, 2005; Catani and Mesulam, 2008; Doricchi et al., 2008; Epelbaum et al., 2008; Geschwind, 1965a, b; Rudrauf et al., 2008b; Rusconi et al., 2010). The concept of a disconnection syndrome, its impact on lesion symptom mapping and on the application of DTI is discussed in detail at several junctures in this thesis.

fMRI is another technique, which, similarly to DTI tractography, cannot be routinely used in clinical settings but has a remarkable potential to give insights into brain-behaviour relationships and functional reorganization in neuronal networks following brain damage (including effects of stroke rehabilitation; Carey and Seitz, 2007; Cramer, 2004; Johansen-Berg, 2007a; Munoz-Cespedes et al., 2005; Zemke and Cramer, 2002; Zemke et al., 2003). Several groups have demonstrated that recovery of motor function following stroke is associated with changes in patterns of brain activation measured by fMRI (Calautti and Baron, 2003; Ward et al., 2006; Zemke et al., 2003). The full understanding of stroke recovery requires insights into both the functional and neuroanatomical mechanisms underlying the various behavioural deficits that can occur and both DTI and fMRI may be important here. To date, combined DTI-fMRI case studies have provided direct evidence that visual, motor and language recovery is associated with structural modifications within the affected neuronal pathways (Heller et al., 2005; Newton et al., 2006; Seghier et al., 2004). For example, Newton and colleagues (2006) used fMRI combined with tractography in healthy volunteers to define pathways within the motor system and then assessed the extent of white matter damage within these pathways in three stroke patients. The derived indices of white

matter damage were subsequently correlated with these patients' functional outcome and motor activation patterns measured by fMRI (Newton et al., 2006). Furthermore, Schaechter et al. (2008), in a study examining a group of heterogeneous chronic stroke patients with damage within the corticospinal tract, demonstrated that the extent of the neuronal lesion determines the extent of reorganization within sensorimotor cortex.

Importantly, these multimodal studies strongly indicate that, due to the heterogeneity of stroke patients, the effective rehabilitation of specific motor and cognitive deficit may require case-by-case evaluation of which brain regions and functions are relatively spared. In addition, these studies provide strong evidence that combined DTI-fMRI is an important tool not only in clinical research but also in basic cognitive neuroscience research (for brain-behaviour mapping). Based on recent developments in neuroimaging, it can be expected that multimodal imaging studies in patients with different neurocognitive deficits will help to define the role of various brain regions in specific cognitive processes and thus provide insights into brain-behaviour relationships and their relation to functional-cognitive theories.

COGNITIVE NEUROPSYCHOLOGY

Cognitive psychology aims to comprehend the functional mechanisms of human cognition. To accomplish this, one of its prominent branches, cognitive neuropsychology is concerned with furthering our understanding about brain-behaviour relationships through the analysis of lesion data from brain-damaged patients with specific cognitive deficits (Coltheart and Caramazza, 2006). According to Ellis and Young (1988), authors of the first subject-specific textbook in this field, cognitive neuropsychology has two aims: (1) to use normal cognition models to guide our understanding of the impact of lesions on the cognitive performance in brain-damaged patients and (2) to use patients' data reflecting the pattern of

impaired cognitive performance to draw models of normal cognitive processes (Ellis and Young, 1988, 1996). In other words, despite the fact that cognitive neuropsychologists work primarily with brain-damaged individuals, the ultimate objective of their research is concerned with how the normal human brain works (i.e. inferring models and neuronal substrates underlying human cognitive processes). Specifically, cognitive neuropsychologists study the neuronal substrates and functional architecture of human cognition by examining how and why cognitive abilities such as perception, attention, language, learning, memory, decision making, problem solving thinking and reasoning etc., are broken in neurological patients (Coltheart and Caramazza, 2006).

The method of inferring about brain-behaviour relationships based on the link between a lesion and the patient's cognitive impairment (lesion-symptom mapping), was pioneered in 19th century by neurologists including Broca (1861) and Wernicke (1874) and back then was based on post-mortem brain dissections. Modern cognitive neuropsychology is supported by non-invasive living-brain imaging techniques suitable to study both normal anatomy and injury/disease-related changes. Neuroimaging techniques that elucidate the structure and function of the human brain in both normal and clinical populations, together with the development of computational cognitive science, have revolutionized the approach to understanding human cognition and stimulated the debate whether using lesion data to infer brain function is perhaps outdated. Although cognitive neuropsychology has significantly evolved since the time when researchers had to wait for the death of patients to examine their damaged brains, some researchers question whether cognitive neuropsychology is a remnant of the past and, in the era of recent advances in cognitive neuroscience and computational modelling, whether the field has anything new to add about "functional architecture of cognition" (e.g., see Coltheart, 2010; Patterson and Plaut, 2009; Plaut and Patterson, 2010).

Such arguments are often based on the concern that cognitive neuropsychology can be highly dependent on single-case studies and on the use of simple dissociations in cognitive performance (see for example Patterson and Plaut, 2009). But such a view of modern cognitive neuropsychology neglects the most recent addition to the research tools available, which now include advanced lesion-symptom mapping approaches (see described below). These emerging techniques can provide direct answers to the major concerns brought up by Patterson and Plaut (2009) and others.

Despite the fact that in the last few decades the neuroimaging techniques such as fMRI, EEG (electroencephalography), MEG (magnetoencephalography) and TMS (trans-cranial magnetic stimulation) have provided new opportunities to assign discrete cognitive functions to specific brain regions and neuronal networks, the lesion-symptom mapping approach remains an extremely powerful and useful tool. Functional MRI measures changes in blood flow enabling the investigator to identify brain regions with the blood flow associated with specific behaviour. While the temporal resolution of fMRI is limited, it remains superior to any lesion methods. However what fMRI cannot tell us is whether a particular brain region is essential to perform given cognitive function (for further discussion about fMRI and study of human cognition see Coltheart, 2006; Henson, 2005; Page, 2006; Shallice, 2003) and this is where lesion data can provide more direct evidence. EEG and MEG offer even better temporal resolution than fMRI but compared to both fMRI and lesion method, these techniques suffer from poorer spatial resolution (Hamalainen et al., 1993; Hari et al., 2000; Hari et al., 2010; Srinivasan, 2007). Conversely, TMS a technique that noninvasively induces transient changes in brain activity that provides both good temporal and spatial resolution. Importantly, TMS allows direct inferences about the necessary relationships between brain activity and cognitive functions (Pascual-Leone et al., 2000; Sack,

2006; Walsh and Cowey, 2000). Unfortunately, though, the effects of TMS are not fully understood and the main concern is that TMS not only disrupts the function of the studied region but also evokes a wider spread of either excitatory or inhibitory changes, causing potentially unwanted and poorly understood secondary changes in brain activity (Driver et al., 2010; Pascual-Leone et al., 1999; Pascual-Leone et al., 2000; Walsh and Cowey, 2000).

In summary, the main advantages of traditional approaches in cognitive neuropsychology (i.e. lesion-symptom mapping methods based on high resolution structural imaging) are that (i) the role of the specific brain region can be inferred directly based on alterations in behaviour or specific cognitive deficits, as opposed to the correlatory approaches used by functional neuroimaging, and (ii) these methods also provide good spatial resolution. Nevertheless, lesion-symptom mapping needs to be planned and executed with caution, while taking into account several factors that could potentially confound the findings. As my thesis is concerned specifically with lesion-based analyses of cognitive function, these issues are discussed in detail in the next section of this chapter, which is exclusively devoted to different lesion-symptom mapping methods. The following research chapters of my thesis focus on understanding both the structural and functional organization of human brain networks underlying visuospatial attention and the studies exclusively utilize lesion-symptom mapping methods. As there is also a large body of evidence from other neuroimaging approaches including TMS (e.g. Battelli et al., 2009; Pascual-Leone et al., 1994) and fMRI (e.g. Corbetta and Shulman, 2002; Galati et al., 2000; Shulman et al., 2010) concerning human attentional networks, one of the aims of the General Discussion chapter (Chapter 6) is to contrast and compare different approaches to studying the brain networks subserving visuospatial attention.

The last important point that should be made here is that cognitive neuropsychology

not only has a great potential to advance our basic understanding of human cognition but also has potential tangible application in the areas of clinical assessment, understanding functional recovery and rehabilitation. As cognitive neuropsychologists work towards creating models of specific cognitive domains, these in turn have a potential to be incorporated and developed into tools for comprehensive assessment of cognitive deficits in brain-damaged patients. Some examples of such cognitive assessment tools include the Hayling and Brixton tests evaluating executive functions (Burgess et al., 1997), the PALPA battery for assessing language (Kay et al., 1992), the BORB object recognition battery (Riddoch and Humphreys, 1993) and the BCoS (Birmingham Cognitive Screen; http://www.BCoS.bham.ac.uk). Importantly, better assessment tools can help to provide a more comprehensive cognitive profile of patients, improving lesion-symptom mapping methods and feeding back to more complete and improved models of human cognition. I will return to this argument in the next section of this chapter, specifically addressing the implications and limitations of lesion-symptom mapping approaches but please note that this issue is also addressed throughout all the research chapters (Chapter 2-5). Another practical advantage of comprehensive cognitive assessment tools is the ability to diagnose and monitor a patient's recovery, which, combined with brain imaging, provides an opportunity to infer which patients are likely to show functional recovery of specific cognitive domains (see Chapter 5 for further discussion; see also Karnath et al., 2011; Phan et al., 2010). Finally, cognitive neuropsychological models of human cognition influence not only the development of assessment tools but they can also guide rehabilitation within specific cognitive domains, targeted either at an affected module or at by-passing the functional deficit (for further discussion and examples see Humphreys and Riddoch, 1994b; Whitworth et al., 2005).

LESION-SYMPTOM MAPPING: NEUROIMAGING OF COGNITIVE DEFICITS

In the last decade statistical approaches to voxel-based mapping of brain-behaviour relationships, combined with advances in brain imaging, have revolutionized cognitive neuropsychology by providing research tools suitable for merging cognitive models with accurate localization of the associated brain networks – most notably by mapping brain lesions in neuropsychological patients to their key symptoms. I will now review these developments focusing on voxel-based lesion-symptom mapping (VLSM; Bates et al., 2003; Rorden et al., 2007b) and voxel-based morphometry (VBM; Ashburner and Friston, 2000). Finally, to complete this general introduction to the thesis, I conclude with a brief introduction to lesion-symptom mapping of visuospatial attention networks as this will be the main focus of the following empirical chapters.

Cognitive neuropschology was born out of studies based on intriguing single cases where individual associations were examined between the cognitive deficits exhibit by an individual patient and the location and extent of his/her brain damage (often evaluated post-mortem). It is undisputable that these simple lesion-symptom analyses provided important insights into the functional organization of the human brain, including examples such as that of Broca (1861) assigning speech production to left ventral frontal lobe. The subsequent accessibility of structural neuroimaging methods brought an important shift from single case reports to group studies and popularized the concept of a neurological syndrome (i.e. grouping patients based on similarities in their behavioural problems and patterns of lesions). This shift was imperative as significant limitations in inferring brain-behaviour relationships based on single case studies exist due to (i) individual differences in the overall organization of the brain (Amunts et al., 2004) and (ii) the fact that it is rare that brain injury results in a single cognitive deficit, making it difficult to assign a region to particular cognitive function

from one lesion in a given patient (as the lesion may affect more than the critical area, how can non-critical areas be distinguished?). Another criticism of lesion methods with single cases is the assumption that specific cognitive functions are subserved by discrete anatomical regions (the “modularity assumption”), while in fact many cognitive functions depend on large and widely distributed networks (Farah, 1994; Rorden and Karnath, 2004). In other words, a given cognitive deficits following a localized lesion might result from disruption to a different region within a network and this cannot be appreciated when looking at single case data. If we also take into account that individual patients may suffer from multiple cognitive deficits while differing in the location and extent of their lesion depending on the underlying aetiology, then the merit of group studies seems undeniable. But despite the fact that group studies provide an important solution to limitations in lesion-symptom mapping, some researchers argue that only single-case studies provide valid insights as individual lesions and cognitive impairments are unique (e.g. Caramazza, 1986; see also Parkin, 1996).

As discussed above, an important constraint on lesion-symptom mapping is associated with “modularity assumption”. However, at least to some extent this can be overcome by studying large not preselected patient populations, using adequate statistical models and taking into consideration the disconnection syndrome concept (i.e., accounting for the fact that even small white matter lesions may affect large scale cortical networks resulting in cognitive deficits; Catani, 2007; Catani and Ffytche, 2005; Rudrauf et al., 2008a; Rudrauf et al., 2008b). The other shortcomings of lesion-symptom mapping are linked to the aetiology of the brain injury and associated tissue vulnerability, brain plasticity and limitations related to type of neuroimaging data used. For example, the location and extent of a lesion will depend on the aetiology, as different areas of the brain vary in their vulnerability (e.g., depending on where they fall in relation to blood supply). As a result lesions are not randomly distributed

and some areas are damaged more often in specific patient groups. This means that some findings on brain behaviour relationships might be influenced by patient selection (Caviness et al., 2002; Heinsius et al., 1998; Rorden and Karnath, 2004). However, the difficulties with interpreting the results of lesion analyses can be averted by including data from control patient groups with the same aetiology but without the critical cognitive deficit and by using statistical approaches combined with examining large patient populations selected using broad inclusive criteria. These points are further discussed below with respect to different lesion method approaches. The final point that should be raised here, however, is brain plasticity and the possible structural and functional changes that may take place following brain damage. Due to the changes taking place as a patient recovers (or degenerates), it is important to take into account time since injury (in terms of both cognitive evaluation and brain imaging) when inferring brain function from lesion data. At the acute stage some brain areas might be structurally intact but functionally disabled due to disrupted perfusion and these temporarily malfunctioning regions might contribute to the cognitive deficits (see Hillis et al., 2002; Hillis et al., 2006; Ticini et al., 2010 for examples on contribution of cortical malperfusion to visuospatial and language deficits). At the chronic stage perfusion might be restored, however cognitive performance may then be often affected by further infarction and/or changes associated with brain plasticity (see also Rorden and Karnath, 2004). These important methodological considerations are further explored in respect to recovery from allocentric and egocentric neglect in Chapter 5.

Although sometimes viewed as relic of the past, lesion- based analyses of cognitive function still have much to offer not only cognitive neuropsychology but also neuroscience in general. The main advantage of lesion-symptom studies is ability to directly infer the critical involvement of a discrete brain region in specific cognitive functions. This is not the case for

studies based on brain activation such as fMRI for example. Brain activity registered by these techniques only provides evidence that performance on a behavioural task correlates with activation of a certain brain region. Correlatory evidence does not show that a brain region is necessary for the exhibited behaviour since (e.g.) activation may arise due to existing strong neural connections but it may not play a causal role (Henson, 2005; Sarter et al., 1996). Thus, despite their limitations, lesion-symptom mapping studies have a unique ability to both progress and refine our understanding of the structural and functional organization of human brain.

Overlap Mapping

Going beyond single-case based analyses, group studies of lesion-symptom mapping have traditionally relied on the superimposition of lesion maps from groups of patients. The procedure here typically involves creating lesion maps through manual reconstructions/lesion delineation, which are mapped onto schematic templates using anatomical landmarks (Adolphs et al., 2000; Damasio and Damasio, 1989; Knight et al., 1988). Once individual lesion maps are completed and overlay plots created, then conclusions are made based on the region of maximal lesion overlap in relation to the behavioural deficits (Damasio and Damasio, 1989). However, this simple approach fails to take into account that areas of significant overlap may be a direct result of factors other than the common cognitive deficit shared by studied group of patients. For example overlap may reflect increased vulnerability of certain brain areas - such as stroke affecting particular vascular territories (Caviness et al., 2002). Subsequently, a more common and more desirable approach involves the inclusion of a control patient group (without the cognitive deficit of interest but similar in terms of other variables) as well as an experimental group with the key symptoms, and use of a lesion

subtraction procedure - highlighting differences in the lesion pattern between the two groups (Adolphs et al., 2000; Karnath et al., 2002; Rorden and Karnath, 2004). Subtraction plots are frequently used to highlight differences in lesion sites associated with two different cognitive deficits or to control for presence of additional common behavioural impairments or a common aetiology (e.g. Karnath et al., 2003; Karnath and Perenin, 2005; Rudrauf et al., 2008a, Chapter 4). However, studies using lesion overlap and subtraction plots remain limited. One issue is that the data are often treated in a reductionist manner either in the way that behavioural data are used [e.g., categorically dividing patients into those with a specific cognitive deficit and those without ("behaviour-defined groups")] and/or lesion data analyzed [i.e. categorically grouping patients based on a common site of injury, presence or absence of lesion within particular region of interests ("lesion-defined groups")]. In the first case, binary scores can result in the loss of information about the degree of impairment. In the "lesion-defined groups" scheme, the regions of interest are often very broadly defined and then any anatomical sensitivity can be lost. Although there have been successful attempts to semi-automate lesion reconstruction protocols (e.g. using fuzzy clustering, Seghier et al., 2008, or using VBM methods, Chechlacz et al., 2010 [Chapter 2 here]), it should be noted that most traditional lesion symptom mapping studies are based on manual lesion delineation protocols that are susceptible to individual biases and uncertainties in mapping (it is not always clear where a lesion starts and ends and how to map the lesion location onto the template). Thus, taking into account potential problems with defining the lesion, the effects of data reduction and the lack of formal statistical comparisons, the traditional lesion-symptom mapping method has been largely replaced by approaches such as voxel-based lesion symptom mapping (VLSM; Bates et al., 2003) and voxel-based morphometry (VBM; Ashburner and Friston, 2000). These are considered below.

Voxel-based lesion symptom mapping (VLSM)

The new era of lesion symptom mapping has been marked by the application of statistical analyses to lesion data. The term VLSM can be traced to Bates et al. (2003), who first applied the principles of voxel-based analysis procedures used in studies of functional MRI to lesion assessment. Similar to lesion overlap/subtraction methods, VLSM employs either manually delineated or semi-automatically segmented binary lesion maps where each voxel within the brain is assigned to either a spared or damaged (lesioned) category. However, in contrast to lesion overlap/subtraction methods, VLSM makes use of continuous behavioural scores and statistical approaches to any analysis. For each voxel, patients are divided into two groups based on the presence or absence of a lesion. The behavioural scores for the groups are then compared using t-statistics and finally a statistical map is produced in which each voxel is assigned the value of the statistcal test comparing the two groups (Bates et al., 2003). More recently, other authors have argued for other (e.g., non-parametric) statistics being applied when this approach is adopted, depending on the particular study (Rorden et al., 2007a; Rorden et al., 2009; Rorden et al., 2007b). In particular, Rorden et al. (2007a,b; 2009) suggested using Welch's t-test, which does not assume equal variance between groups, along also with non-parametric tests (e.g., the Brunner-Munzel test), which do not make assumptions about the distribution of the data. Finally, it should be noted that while typical VLSM analyses are based on a single behavioural score reflecting a specific cognitive deficit, more complex types of analyses can be implemented - including factoring out the effects of covariates other than main behavioural score (e.g. age, lesion size, secondary behavioural measures etc.). This is of particular importance as performance on the task used as a primary measure of any cognitive deficit may be driven by different

behavioural problems that co-vary with the factors of interest within a given group of patients. Not taking these co-varying factors into account may be misleading.

Voxel-based morphometry (VBM)

Another advanced method of lesion-symptom mapping is voxel-based morphometry (VBM) that associates voxel-by-voxel continuous local differences in tissue composition, grey and white matter tissue density, with continuous behavioural data (Ashburner and Friston, 2000). It can be argued that VBM offers the next step in moving away from categorical to non-categorical approaches when inferring cognitive function from lesion data, by linking the magnitude of any cognitive deficit to the magnitude of tissue change in different brain regions (Ashburner and Friston, 2000; Mechelli et al., 2005). VBM has a clear advantage over other procedures as it provides a resolution to the biggest challenges faced by lesion symptom mapping: defining the cognitive impairment, lesion normalization and lesion segmentation. Treating patients in a categorical manner (deficit vs no deficit) results in not only a significant loss of information about the degree of impairment but also forces diagnoses that may not be as straightforward. For instance, some syndromes are characterized by symptoms that can fractionate in a given group of patients and/or co-vary with other behavioural deficits (e.g., different components of the neglect syndrome, including ego- vs. allocentric neglect, see Chechlacz et al., 2010 [Chapter 2 here] and Verdon et al., 2010; spatial neglect vs. visual extinction, Chechlacz et al., 2012 [Chapter 3 here]; neglect vs. simultanagnosia, Chechlacz et al., 2011 [Chapter 4 here]). To overcome this problem, analyses of covariance can be implemented in VLSM. However, VBM, based on the general linear model (GLM), offers a more flexible framework that permits a variety of different statistical tests including: group comparisons, correlations with covariates of interests, the

exclusion of other covariates (age, gender, lesion size) and analyses of complex interactions between different effects of interest (Ashburner and Friston, 2000).

Any type of group analysis based on lesion data requires registration to a common reference (e.g., the MNI space for lesion normalization). In the case of manual lesion delineation, which is used to produce binary lesion maps for both lesion overlap/lesion subtraction and VLSM analyses, lesion registration and lesion segmentation (marking the extent of brain injury) are achieved in one step as the lesions are drawn on high resolution standard MNI template. This procedure is labour intensive as well as subject to human error and individual biases. In contrast, both semi-automated lesion reconstruction protocols and VBM use automated registration i.e. spatial normalization. Spatial normalization involves registration of individual brain scans to the MNI template. Although some of the earlier automated methods struggled with lesioned brains and therefore were heavily criticised, recent advances have eradicated these setbacks (see Brett et al., 2001; Crinion et al., 2007; Shen et al., 2007). One such method transforms brain scans into the standard MNI space using a unified-segmentation procedure (Ashburner and Friston, 2005), which has been shown to be optimal for spatial normalization of lesioned brains (Crinion et al., 2007). The unified-segmentation procedure involves tissue classification based on the signal intensity in each voxel and on a-priori knowledge of the expected localization of grey matter (GM), white matter (WM), cerebrospinal fluid (CSF) in the brain, along with the assignment of an extra class to account for other sources of signal variability. The procedure then iteratively segments the tissues and warps them onto standard MNI space. The unified-segmentation procedure results in classified tissue maps representing the probability that a given voxel 'belongs' to a specific tissue class. The segmented GM and WM maps may then be used in the VBM statistical analyses to determine voxel-by voxel relationships between brain damage

and cognitive deficits. Prior to this final step, each of the segmented scans can be visually inspected to assess whether segmentation and normalisation is successful. The main advantage of automated registration and segmentation is that these procedures are not prone to individual bias, as they do not require decisions about the extent of lesion (there is no binary classification of each voxel within the brain as intact or damaged). Instead of this, the segmented images (GM and WM maps) represent the likelihood of each voxel being the classified tissue based on the intensity in the original image; for example, an abnormal GM tissue would be presented by a lower intensity/probability value than normal. Thus, lesioned brain tissue is typically mapped with a reduced likelihood of representing either grey or white matter due to the change in signal intensities caused by brain damage.

Lesion-symptom mapping of visuospatial attention

The external world constantly bombards us with immense amounts of sensory information. Consequently, effective functioning requires cognitive abilities able to deal with such overwhelming stimulation to prevent sensory overload. The mechanisms put in place to minimize sensory overload are collectively described as attention. Visual attention ensures that we are able to selectively focus and process subsets of the visual scene while ignoring the rest. A distributed neuronal network of frontal and parietal areas, the fronto-parietal network, has been implicated in controlling and allocating visual attention (Corbetta and Shulman, 2002; Mesulam, 1981). Many important insights into the functional and structural organization of visuospatial attention networks come from neuropsychological studies examining patients with a variety of cognitive deficits. Such studies can provide important converging evidence, adding to animal studies and providing important insights into data from functional neuroimaging studies in healthy controls.

The research work included in this thesis examines the organization of visuospatial attention networks based on advanced lesion symptom mapping approaches. In addition, it strives to provide compelling evidence that, in order for lesion methods to infer valuable information about brain function, the method needs to be tailored to the demands of the study in terms of not only questions asked but also patient population, sample size and type of both neuroimaging and behavioural data available. All projects presented here are centred on the relationship between structural changes following brain injury, mainly stroke and visuospatial attention deficits. The analyses focus on the grey and white matter substrates of the heterogeneous impairments associated with visual neglect[1], visual as well as tactile extinction[2] and simultanagnosia[3]. These particular syndromes have been examined because they not only represent deficits affecting different aspects of visual selection but they are also likely to be functionally related and frequently can be present in the same patient. The neuroanatomy of these syndromes has been previously examined but prior studies have often relied on manual lesion depiction, binary data, small groups of patients or case studies, and they typically did not control for confounding factors or multiple symptoms. Not surprisingly, the findings have been often controversial with different research groups having strong but diverse opinions. For example some have argued that neglect is linked to relatively anterior damage (including superior temporal gyrus and insula, e.g., Karnath et al., 2001), while others have argued that it is linked to lesions within posterior parietal cortex (Mort et al., 2003). The results presented in my thesis suggest a way of reconciling at least some of the previous disparate findings. The novelty of my work is that I use information from segmented grey and

[1] Visual neglect refers to the lack of spatial awareness of side of space contralateral to the side of brain damage (see Heilman and Valenstein, 1979).
[2] Extinction refers to the drop in a patient's ability to detect a contralesional stimulus, when that stimulus is presented along with a competing item on the ipsilesional side (Bender and Teuber, 1946; Critchley, 1953; Wortis et al., 1948).
[3] Simultanagnosia refers to the impaired spatial awareness of more than one object at time (see Rizzo and Vecera, 2002).

white matter tissue combined with diffusion tensor imaging (DTI) to decompose neural substrates of visuospatial attention deficits in neurological population. Notably, the main approach to lesion-symptom mapping employed in all the studies presented here is VBM, as this method is based on robust statistical tests and allows the reliability of the association between lesion site and any behavioural deficit to be assessed. In addition, VBM can make it possible to control for various confounding factors that potentially might affect the measured cognitive performance.

Chapters 2-4 decompose the neural substrates of different aspects of visouspatial attention. These chapters are presented in the form of self-contained manuscripts, each including a lengthy introduction and discussion. Therefore, I will not attempt to repeat all this information here. The final chapter of my thesis (Chapter 6) also presents extensive summary and discussion about how all the different findings together advance our understanding of the structural and functional organization of visuospatial attention, with particular emphasis on the relationship between grey matter dysfunctions and white matter disconnections. Chapter 5 is unique is terms of both the addressed research question (the recovery of function) and the type of data used. Although the study in Chapter 5 examines the neural substrates of acute visuospatial deficits, namely allocentric versus egocentric neglect as well as the relationship between these two symptoms, the main question is concerned with the prognosis for outcome following stroke based on clinical scans acquired at an acute or sub-acute stage. More specifically, as persistent visuospatial deficits are often associated with overall poor functional outcome (Buxbaum et al., 2004), it is important to delineate which lesions are associated with persistent symptoms and which with recovery of function. The unique aspect of this particular study is that it employs neuroimaging data sets obtained as a part of routine clinical practise i.e. CT scans acquired as a part of clinical diagnosis and behavioural data

collected as a result of a large multicentre clinical study, the Birmingham University Cognitive Screen. Chapter 5 is also presented as a self-contained manuscript.

Overall, the data presented in this thesis not only provide further evidence that visuospatial attention depends on a large network of cortical areas interconnected by long association white matter pathways, but they also provide important insights into the structural and functional organization of this network by neuroanatomical decomposition of different visuospatial deficits. My work highlights both differences and commonalities across various spatial attention deficits. The empirical chapters presented here clearly demonstrate that not only the different pattern of grey matter lesions but also the laterality of white matter disconnections in individual neuropsychological patients determine the degree to which visual processing and spatial attention are disrupted and thus the nature of cognitive symptoms observed in patients.

CHAPTER 2:

SEPARATING NEURAL CORRELATES OF ALLOCENTRIC AND EGOCENTRIC NEGLECT: DISTINCT CORTICAL SITES AND COMMON WHITE MATTER DISCONNECTIONS[4]

[4] This chapter is published in Cognitive Neuropsychology: Chechlacz M, Rotshtein P, Bickerton WL, Hansen PC, Deb S, and Humphreys GW. Separating neural correlates of allocentric and egocentric neglect: Distinct cortical sites and common white matter disconnections. *Cognitive Neuropsychology*, 27 (3):277-303, 2010.

ABSTRACT

Insights into the functional nature and neuroanatomy of spatial attention have come from research in neglect patients but to date many conflicting results have been reported. The novelty of the current study is that we used voxel-wise analyses based on information from segmented grey and white matter tissue combined with diffusion tensor imaging to decompose neural substrates of different neglect symptoms. Allocentric neglect was associated with damage to posterior cortical regions (posterior superior temporal sulcus, angular, middle temporal and middle occipital gyri). In contrast egocentric neglect was associated with more anterior cortical damage (middle frontal, postcentral, supramarginal and superior temporal gyri) and damage within sub-cortical structures. Damage to intraparietal sulcus (IPS) and the temporo-parietal junction (TPJ) was associated with both forms of neglect. Importantly, we showed that both disorders were associated with white matter lesions suggesting damage within long association and projection pathways such as the superior longitudinal, superior fronto-occipital, inferior longitudinal and inferior fronto-occipital fascicule, thalamic radiation and corona radiata. We conclude that distinct cortical regions control attention (i) across space (using an egocentric frame of reference) and (ii) within objects (using an allocentric frame of reference), while common cortical regions (TPJ, IPS) and common white matter pathways support interactions across the different cortical regions.

INTRODUCTION

Patients with unilateral visual neglect fail to attend to stimuli presented on the side of space contralateral to their lesion (Heilman and Valenstein, 1979). These patients provide an important source of evidence about the brain regions necessary to the allocation of attention to space. The nature of the ‘space’ that is neglected may vary across patients. For example, some

patients demonstrate neglect based on where stimuli fall in relation to their body (egocentric neglect; Doricchi and Galati, 2000; Riddoch and Humphreys, 1983), while others neglect parts that fall on the contralesional side of objects irrespective of the positions of the objects relative to the patient (allocentric neglect; Doricchi and Galati, 2000; Kleinman et al., 2007; Olson, 2003; Walker et al., 1996; Walker and Young, 1996). Egocentric and allocentric neglect can dissociate across patients (Marsh and Hillis, 2008) and can even occur on opposite sides of space within single patients with bilateral brain lesions (Humphreys and Riddoch, 1994a, 1995). Understanding the neural regions that control spatial attention may depend on separating the circuits supporting the attention (i) across space in relation to the body and (ii) across parts within objects.

There have been several prior attempts to use data from neglect patients to make inferences about the neural substrates of spatial attention, and the results have proved controversial. Some findings suggest that damage to the temporo-parietal junction (TPJ) is critical in developing neglect syndrome (Leibovitch et al., 1998; Vallar, 2001; Vallar et al., 2003). A second line of studies report that lesions to the superior temporal gyrus (STG), insula, pulvinar and basal ganglia are crucial (Karnath, 2001; Karnath et al., 2001; Karnath et al., 2004; Karnath et al., 2002; Karnath and Perenin, 2005; Karnath et al., 2005). A third set of findings highlights damage to angular gyrus and the medial temporal lobe (parahippocampus; (Mort et al., 2003). Finally, some researchers have tried to resolve the controversies on critical cortical regions associated with neglect by suggesting that neglect is a disconnection syndrome (Bartolomeo et al., 2007; Doricchi and Tomaiuolo, 2003). This hypothesis is supported by findings from single case studies (Thiebaut de Schotten et al., 2005; Urbanski et al., 2008) and pathway-of-interest analyses (Bird et al., 2006; He et al., 2007; Thiebaut de Schotten et al., 2008; Thiebaut de Schotten et al., 2005; Urbanski et al., 2008) showing that

neglect is associated with damage to the superior longitudinal (SLF; He et al., 2007; Thiebaut de Schotten et al., 2008), the inferior longitudinal (ILF; Bird et al., 2006) and the inferior fronto-occipital fasciculi (IFOF; Urbanski et al., 2008). Thus taken together prior neuroanatomical analyses are unclear about the neural substrates of neglect and, consequently, about the neural areas necessary to the control of spatial attention. Previous studies have also not provided comprehensive information about the extent of grey versus white matter contributions to the functional deficits apparent in neglect patients.

One potential explanation for inconsistencies in the literature is that most studies have ignored the heterogeneous nature of the deficit whilst using different behavioural measures to define neglect. For example, in some studies neglect has been either defined largely in terms of performance on line bisection tasks or deficits pooled across line bisection and cancellation (Bird et al., 2006; Mannan et al., 2005; Mort et al., 2003), while in others neglect has been defined using a battery of tasks but all including some degree of spatial exploration (Karnath et al., 2004; Karnath et al., 2002). While exploration tasks such as line cancellation require that multiple stimuli are coded in relation to the patient (e.g., using an egocentric reference frame), tasks such as line bisection could reflect either separate coding of the perceived ends of the lines in relation to the patient (i.e., egocentric spatial coding) or perception of the line as a single object (i.e., allocentric spatial coding), which make it less clear how a deficit may arise in a given patient (Humphreys and Riddoch, 1994a, 1995).

Vallar and colleagues (Vallar et al., 2003) propose that spatial coding within an allocentric frame of reference depends on processing in the ventral visual stream while egocentric spatial coding operates within the dorsal visual stream. Data from single case studies however suggest that allocentric neglect may link to damage in both dorsal (occipital-parietal) and the ventral (occipital-temporal) areas (Doricchi and Galati, 2000; Walker et al.,

1996; Walker and Young, 1996). There have been previous attempts to distinguish the neuroanatomical basis of these putative forms of neglect using groups of patients. Following Binder et al.'s (1992) suggestion that different neglect symptoms may be associated with damage to discrete brain areas Rorden et al. (2006) compared neglect patients diagnosed from cancellation tests with and without additional line bisection deficits and found that additional poor performance on line bisection was associated with relatively more posterior brain lesions (Binder et al., 1992; Rorden et al., 2006). These two prior studies hypothesized that performance on line bisection and cancellation tasks represent two types of neglect. As we have noted, it is not clear that this is necessarily the case. Moreover, the contrast involved comparing patients with problems on bisection plus cancellation relative to those with problems on cancellation alone. This leaves open the possibility that any contrast reflects the magnitude of the problem, not a difference between different types of neglect. Therefore, this fails to establish if there are distinct patient groups or whether patients with additional deficits have larger lesions. In addition to this, Rorden et al. (2006) used data derived from a pre-selected group of 22 patients with left spatial neglect following right brain lesions; it is not clear from this whether the lesions separate these patients from 'control' patients, who might have similar lesions but do not present with neglect.

Hillis et al. (2005) reported that abnormalities in the right STG were associated with allocentric neglect while damage to the right angular gyrus was linked to egocentric neglect. Medina et al. (2009) argued that egocentric neglect is associated with abnormal function within the supramarginal and superior temporal gyri, while allocentric neglect is associated with dysfunction of middle-superior occipital regions and posterior temporal cortices. Unfortunately the functional contribution of the STG is inconsistent across these studies reported by the same research group, while the contribution of the angular and supramarginal

gyri to egocentric neglect did not replicate. One advantage of these two reports lies in their use of different imaging modalities, including perfusion and diffusion imaging, the application of a comprehensive battery of neglect tests suitable for contrasting different neglect symptoms, and inclusion of a large number of patients (50 and 171 respectively) - though the studies were limited to patients with ischemic infarct within the right hemisphere. Both studies relied largely on manual delineation of the abnormal tissue and demarcation of a lesion was done on a different brain template without applying any formal registration procedure. Such protocols are not only labour-intensive but also susceptible to individual biases and uncertainties in mapping as it is not always clear where a lesion starts and ends and how to map the lesion location onto the template. A further limitation of using manual lesion delineation is that is does not capture changes in brain tissue due to atrophy, which may be important given that age influences the severity of neglect following stroke (Gottesman et al., 2008). In addition, the spatial resolution of the main analyses was defined categorically by different Brodmann areas, masking potential functional dissociations within a single area and by including only patients with ischemic infarct confined to right hemisphere. One further point is that there were no formal statistical comparisons between the two types of neglect and the analysis was restricted to abnormalities of the grey matter. Thus information about the contribution of damage in white matter to the different neglect symptoms is still unclear[5].

[5] Other potential limitations of previous studies are (i) biased patient selection (based on behaviour or lesion location) and (ii) the analyses that were conducted on the neuroimaging data. In particular, earlier studies have used categorical distinctions between patients with and without neglect, and thus fail to reflect the severity of the problems in different patients. Furthermore, lesions demarcations have been performed manually in an observer-dependent manner using different template images and different registration and normalization protocols (Karnath et al., 2004b; Mort et al., 2004; Mort et al., 2003). This introduces a researcher confound in registration and normalisation. Manual delineations also typically do not include tissue atrophy and other age related changes along with the lesion, making the analyses insensitive to the contribution of such structural changes to the functional deficit in patients (Gottesman et al., 2008).

In one other study distinguishing between different neglect symptoms, Verdon et al (2010) argued for three components within the syndrome: (1) a perceptual deficit (assessed through tasks such as text reading and line bisection), (2) a component reflecting attention within an allocentric reference frame (missing the contralesional side of words, missing a contralesional gap in circles), and (3) a component reflecting exploration in egocentric space (missing complete targets on the contralesional side of a page). In contrast to studies relying solely on reduction approaches to behavioural data (i.e. categorically dividing patients to those with neglect and without neglect), these authors employed observer dependent lesions demarcations but used voxel-based lesion-symptom mapping based on continuous behavioural scores alongside traditional statistical comparison between lesions in different categorically-defined groups. Subsequently they linked the different neglect deficits to (1) the right inferior parietal lobe, (2) lesions to inferior temporal regions, and (3) the right dorsolateral prefrontal cortex. The site linked to allocentric lesions was difficult to establish however, with the main peak occurring in white matter. Moreover these authors did not directly examine white matter vs grey matter contributions to different components of the neglect syndrome, nor did they use targeted DTI analyses to assess the integrity of specific white matter tracts (though they noted that damage to white matter tracts were likely associated with severe neglect).

In the current study we attempted to go beyond these previous lesion-symptom analyses in several ways, but most notably by combining voxel-based analyses with DTI imaging of white matter tracts, along with using behavioural measures from a single task sensitive to both egocentric and allocentric neglect symptoms. Using these combined procedures, we aimed to delineate common and dissociable brain structures involved in allocentric and egocentric neglect, dissociating the contribution of white as well as grey

matter changes. Importantly, we used observer-independent voxel-based analysis combined with robust statistical methods to assess the association between the behavioural deficits and the underpinning grey and white matter lesions. We also used both parametric and non-parametric approaches, enabling a comparison to be made between these methods. In addition, we tested allocentric and egocentric neglect in patients with chronic deficits, when patterns of impairment are stabilised after any secondary damage and reorganization of neuronal networks. Our study contrasts with previous reports not only in terms of our image analysis methods but also in employing an unbiased sample (patients were not pre-selected based on clinical, anatomical and neuropsychological criteria) and we looked for common structure-function relationships across the whole brain, irrespective of aetiology (stroke, degenerative changes). The whole-brain methods give us an opportunity to incorporate age-related changes such as atrophy into the analysis of the syndrome. The overall approach enables us to ask a question different to that posed hitherto, about what neuronal substrates are necessary to the allocation of attention to allocentric and egocentric space rather than confining our question to the neuropathology of neglect following stroke.

The severity of neglect symptoms here was assessed using a theoretically motivated behavioural test similar to that used by (Ota et al., 2001) in order to simultaneously distinguish allocentric and egocentric neglect. This allowed us to control for variability in patients' behaviour due to differential task demands, test conditions and stimuli that could potentially arise when using measures of the two types of neglect in different tasks. In addition the analysis treated the behavioural measurements as continuous variables rather than as categorical scores, which increased both the ability to tease apart the two different types of neglect and the sensitivity for detecting brain-behaviour associations.

Finally, white matter deficits have only been analysed previously using small groups of individuals, pathway of interest analysis and/or having been looked at separately from grey matter lesions. We present the first group-level analysis of white matter changes and, by characterising both white and grey matter damage, we are able to review the relations between each type of change and how any lesions may link to contrasting forms of neglect. We highlight both common and distinct areas of cortical and sub-cortical lesions associated with allocentric and egocentric neglect, along with common white matter damage across all neglect patients. The relations between these deficits and multi-component accounts of visual neglect are discussed in relation to an overall computational framework for understanding spatial selection and neglect.

METHODS

Participants

A total of forty-one patients were recruited for this study (30 males and 11 females), with ages ranging from 32 to 85 years (mean age 63 years). All patients had acquired brain lesions (stroke, carbon monoxide poisoning, degenerative changes), were at a chronic stage (> 9 months post injury) and had no contraindications to MRI scanning. No other exclusion criteria were used. All patients participating in this study were recruited from the panel of neuropsychological volunteers established in the Behavioural Brain Sciences Centre at the School of Psychology, University of Birmingham, and all patients had been subject to the Birmingham University Cognitive Screen (BUCS). All patients but 4 had normal or corrected-to-normal vision. Clinical and demographic data for all the patients are shown in Supplementary Table 1 (Appendix 1). These data include analyses demonstrating the test/re-test reliability of the measures of neglect, along with the common pattern of deficits found

when converging measures of allocentric and egocentric neglect were taken. Two patients had left and 2 had right visual field deficits. However, as eye and head movements were not restricted in the behavioural task, we included the data from these patients. As listed in Supplementary Table 1 (Appendix 1), three patients had lesions caused by carbon monoxide poisoning and five patients had chronic degenerative changes. For the purpose of neuroimaging analyses, we excluded the three patients with carbon monoxide poisoning[6]. In addition, for the lesion reconstruction protocol (see below) we acquired T1 weighted images from 73 healthy controls (40 males and 33 females, mean age 61 years, range 30-87) who had no history of stroke, brain damage or neurological disorders. All participants provided written informed consent in agreement with ethics protocols at the School of Psychology and Birmingham University Imaging Centre (BUIC).

Cognitive assessment

The neglect assessment was based on Apple Cancellation task developed as a part of Birmingham University Cognitive Screen (BUCS; http://www.bucs.bham.ac.uk). The Apple Cancellation task (Figure 1A) is similar to the gap detection task of Ota et al. (2001) and is designed to simultaneously measure egocentric and allocentric neglect. Participants are presented with a page (A4) with 50 apples divided into 5 invisible columns, one middle, one near left, one far left, one near right and one far right. Each column contains 10 complete

[6] One potential weakness with the present approach is that the analysis of the grey matter was based on T1 weighted images. This may underestimate the extent of brain changes (e.g., in acute cases or in patients with carbon monoxide poisoning or degenerative changes). However, all patients included in this study were chronic and out of 41 patients, only three suffered from carbon monoxide poisoning and five from degenerative changes (three of these patients also suffered from different forms of unspecified vascular disease causing additional acquired brain lesions). Three patients with carbon monoxide poisoning were excluded from neuroimaging analyses. All five chronic patients with degenerative changes have defined lesions visible on T1 scan. Furthermore, for most of these patients we have available FLAIR or T2 contrast images and the lesion segmentations and reconstructions based on T1 images have been successfully verified based on FLAIR/T2 contrast (see example in Supplementary Figure 1B,C). Importantly, note that for the white matter we presented VBM style analyses from DTI images (using T2-based contrast images) that confirm the T1 findings.

apples (targets) along with distractors, which are apples with either a left or a right part missing (incomplete apples). Each column is further subdivided into 2 rows (upper and lower parts), and similar numbers of the three types of items (targets and two types of distractors) are present in the upper and lower sections of each column. A page is placed in landscape orientation in the participant's midline. Participants are given 5 minutes and instructed to cross out full apples only. Two practice trials are given before testing.

The maximum achievable score in the Apple Cancellation task is 50. Egocentric neglect is determined by whether patients miss targets (complete apples) on the left or right side of the page. Allocentric neglect is determined by whether patients make false positive responses by cancelling incomplete apples (distractors) where the gap is on either the right or left side of each apple, irrespective of the position of the (incomplete) apple on the page. Cut-offs to classify patients as having egocentric or allocentric neglect were calculated on the basis of asymmetry scores (left vs. right-side egocentric or allocentric errors), using scores from 86 elderly control participants with no history of neurological diseases (35 males and 51 females, mean age 67 years, range 47-88) and were as follows: Egocentric asymmetry for full apples (based on <2.5th percentile) <-2 right side errors or >3 left side errors; allocentric asymmetry for incomplete apples (based on <2.5th percentile) <-1 right side errors or >1 left side errors. The cut-off for total numbers of target omissions i.e. accuracy score was 40/50 (based on <2.5th percentile).

In the majority of previous reports (and also in our study), patients showing neglect predominantly suffered from unilateral deficits on the left side following right brain damage. Therefore we restricted our analyses to left unilateral neglect (i.e., we used left asymmetry scores as main covariates of interest, but right asymmetry scores were also included as separate covariates in all statistical models). The behavioural scores used in the neuroimaging

analyses were classified based on cut offs drawn from the BUCS (i.e. for the covariates used in the statistical models patients missing fewer than 10 full apples and with fewer than 4 left errors on the left of the page or fewer than 3 right errors on the right of the page were assigned a score of 0 for left or right egocentric neglect respectively, while patients with fewer than 2 false alarms to incomplete apples with a gap on the left or right were assigned a score of 0 for left or right allocentric neglect accordingly). Furthermore, in order to account for variation in overall performance affected by general motor and attentional deficits we took the asymmetry score for full apples and divided it by the total number of full apples missed. The normalized scores are shown in Supplementary Table 2 (Appendix 1).

Neuroimaging assessment

Patients and controls were scanned at the Birmingham University Imaging Centre (BUIC) on a 3T Philips Achieva MRI system with 8-channel phased array SENSE head coil. The anatomical scan was acquired using a sagittal T1-weighted sequence (sagittal orientation, TE/TR=3.8/8.4ms, voxel size 1x1x1mm^3). In addition, out of the 41 patients, 19 (including one patient with carbon monoxide poisoning; see Supplementary Table 1, Appendix 1) were scanned using a diffusion tensor imaging (DTI) sequence employing echo planar imaging (64 slices with isotropic 2x2x2 mm^3 voxels, TR=6170ms, TE=78ms). DTI was acquired in 61 gradient directions with a b value of 1500s/mm^2 and 1 volume was acquired with no diffusion weighting (b=0 image).

Image analyses: T1 data

Image pre-processing. All T1 scans (both from patients and controls) were first converted and reoriented using MRICro (Chris Rorden, University of South Carolina,

Columbia SC, USA). Pre-processing was done in SPM5 (Statistical Parametric Mapping, Welcome Department of Cognitive Neurology, London UK). The earlier versions of SPM struggled with normalizing and segmenting brains containing large lesions (e.g. Stamatakis and Tyler, 2005) but here we applied the advanced unified-segment procedure as implemented in SPM5. The brain scans were transformed into the standard MNI space using the unified-segmentation procedure (Ashburner and Friston, 2005), which has been shown to be optimal for spatial normalization of lesioned brains (Crinion et al., 2007). The unified-segmentation procedure involves tissue classification based on the signal intensity in each voxel and on a-priori knowledge of the expected localization of grey matter (GM), white matter (WM), cerebrospinal fluid (CSF) in the brain and an extra class to account for other sources of signal variability, and iteratively segment the tissues and warped them onto standard space. The outputs of this procedure are 3 classified tissue maps representing the probability that a given voxel 'belongs' to a specific tissue class. Note that the segmented images represent the likelihood of each voxel being the classified tissue based on the intensity in the original image; for example, an abnormal GM tissue would be presented by a lower intensity/probability value than normal. The lesioned brain tissue e.g. affected by stroke is typically mapped with reduced likelihood of representing either grey or white matter due to the change in signal intensities caused by brain damage. In the current study we tested only chronic patients and thus in majority of cases the region of the damaged tissue was 'replaced'/ 'filled' by CSF (as shown in Supplementary Figure 1A, Appendix 1). In addition, to avoid misclassification of abnormal tissue as normal, the number of Gaussians per class was restricted to 1 for both GM and WM. We visually inspected each of the segmented scans to assess whether the segmentation and normalisation was successful (for an example see Supplementary Figure 1A). Finally, the segmented images were smoothed with a 12-mm

FWHM Gaussian filter to accommodate the assumption of random field theory used in the statistical analysis (Worsley, 2003). The choice of 12-mm FWHM instead of default 8-mm was based on previous recommendations for single-case comparison studies (Salmond et al., 2002). The pre-processed GM and WM images were further used in the analyses to determine voxel-by voxel relationships between brain damage and the two neglect scores (see below).

Voxel-based morphometry (VBM). Scans from 38 patients (3 patients with carbon monoxide poisoning were excluded from the final analyses see Supplementary Table 1 for details) segmented into individual WM and GM maps (see above for the pre-processing protocol) were used in a further statistical analysis with SPM5, to assess the relationship between WM and GM damage and neglect scores on voxel-by voxel basis. We used parametric statistics within the framework of general linear model (Ashburner and Friston, 2000) and the analyses for WM and GM were carried out separately. In each statistical model we included the scores for left allocentric and left egocentric errors (both extracted from the Apple Cancellation task, see above). This ensured that we could control and formally test common and dissociated neuronal substrates that contribute to these two types of neglect. Additionally, in the statistical model age, handedness and gender as well as scores for right allocentric and right egocentric errors were included as covariates of no interest. The inclusion of right deficit scores was done to avoid biasing the results based on priori assumptions: for example, analyses excluding patients with left deficits limit inferences about any potential contributions of particular brain regions to both left and right deficits. Note that all analyses included neuroimaging data from left and right hemisphere-lesioned patients as well as from patients with bilateral lesions. Dissociating left allocentric from left egocentric neglect was achieved by using exclusive masking, i.e. testing for a change in voxel intensity that correlated with allocentric ($p < 0.001$, uncorrected) but not with egocentric neglect ($p >$

0.05, uncorrected) and vice versa. Common mechanisms were tested using conjunction analyses (Nichols et al., 2005) to highlight changes in voxel intensity that correlated with both egocentric and allocentric neglect at $p < 0.005$ uncorrected. To reduce the likelihood of type 1 errors, we report only clusters that are larger than $100mm^3$ (>50 voxels). Results are reported at the clusters level corrected for multiple comparisons ($p< 0.05$ FWE corrected), unless stated otherwise. The anatomical localization of the lesion sites was based on the Duvernoy Human Brain Atlas (Duvernoy et al., 1991) and the Woolsey Brain Atlas (Woolsey et al., 2008). The brain coordinates are presented in the standardized MNI space.

Lesion reconstruction and non-parametric lesion mapping. In addition to lesion analysis based on a general linear model (Ashburner and Friston, 2000) we also carried out voxel-based lesion symptoms mapping (VLSM) using binary lesion maps and non-parametric statistics (Rorden et al., 2007b). Tissue abnormalities (lesions) were first reconstructed using a voxel-based analysis with SPM5 by comparing each patient's segmented GM and segmented WM to the segmented GM and segmented WM of the 73 healthy controls. Note that in order to objectively delineate brain abnormalities, medical condition (patient, control) was the independent variable while age and gender were modelled as covariates. GM and WM abnormalities were defined as changes of patient from controls that exceeded the stringent threshold of $P < 0.05$ corrected for family-wise error with an extended cluster threshold of at least 100 voxels (larger than ~$200mm^3$). The results were verified against each patient's T1 scans (as well as T2 or FLAIR images if available) and binary maps of GM and WM lesions were created for the next step of analysis (see example in Supplementary Figure 1B,C in Appendix 1). The non-parametric lesion symptom mapping was performed using NPM (Chris Rorden, University of South Carolina, Columbia SC, USA). We used the Brunner-Munzel test (Rorden et al., 2007b) to determine the relationship between lesion

location and neglect scores, separately for GM and WM maps. In the statistical model both Apple Cancellation task scores (i.e., left allocentric and left egocentric errors) were included as covariates in order to separate the neuroanatomy of the two symptom patterns. In the same manner to the VBM analyses, the statistical models included age, handedness and gender as well as scores for right allocentric and right egocentric errors. Results were considered significant at $P<0.05$, FDR corrected. The anatomical localization of the lesion sites was based on the Duvernoy Human Brain Atlas (Duvernoy et al., 1991) and the Woolsey Brain Atlas (Woolsey et al., 2008).

Image analyses: DTI data

Data processing. All DTI data sets were first converted using MRIcron (Chris Rorden, University of South Carolina, Columbia SC, USA) and then analysed using FSL (FMRIB, Oxford UK). First, we used Eddy Current Correction tool to align all volumes (61 images encoding diffusion strength in all different directions and 1 image with no diffusion weighting i.e. b0 volume). Eddy Current Correction, as implemented in FSL, corrects for gradient coil eddy currents distortions as well as for simple head motions using affine registration to a reference volume (b0 volume). Next, the fractional anisotropy (FA) maps were created using DTIFit within the FSL FDT toolbox (Smith et al., 2004). Subsequently, colour-coded orientation maps were generated and the fibre orientation was assumed based on the eigenvector associated with the largest eigenvalue (Basser et al., 1994). On the colour-coded orientation maps red, green and blue colours were assigned to the left-right, anterior-posterior and superior-inferior orientations accordingly (Pajevic and Pierpaoli, 1999). The anatomical localization of specific white matter pathways was based on the MRI Atlas of Human White Matter (Mori, 2005).

Voxel-wise analysis. The analysis of FA maps was carried out with SPM5. We used b0 volume to determine normalization parameters for the FA maps. First, for each participant all images (b0 volume and FA map) were re-aligned. Next b0 volumes of all participants were normalised to the standard T2 template using linear transformations (Friston et al., 1995) based on previously published procedure (Salmond et al., 2006; Thomas et al., 2009). Subsequently FA maps were normalised to a standard space based on the parameters from the processing of b0 volume. In order to restrict the analysis to white matter and ensure that no results were caused by the close vicinity of grey matter, we created binary white matter-specific mask in MNI space using the WFU Pick atlas toolbox in conjunction with SPM5 (Maldjian et al., 2003). This mask was applied to all individual normalized FA maps prior to smoothing of the images. The smoothing was done with 8-mm FWHM Gaussian filter in order to improve the signal-to-noise ratio and to decrease between-subject variability. Finally, a voxel-wise analysis was carried out to investigate the relationship between the decreased anisotropy and neglect scores. We used an identical model, statistical tests and threshold to those used in the analysis of the segmented WM data from the T1 images (see above). Results are reported at the cluster level corrected for multiple comparisons ($p< 0.05$ FWE corrected), unless stated otherwise. The anatomical localization of damage within specific white matter pathways was based on the MRI Atlas of Human White Matter by Mori et al. (2005).

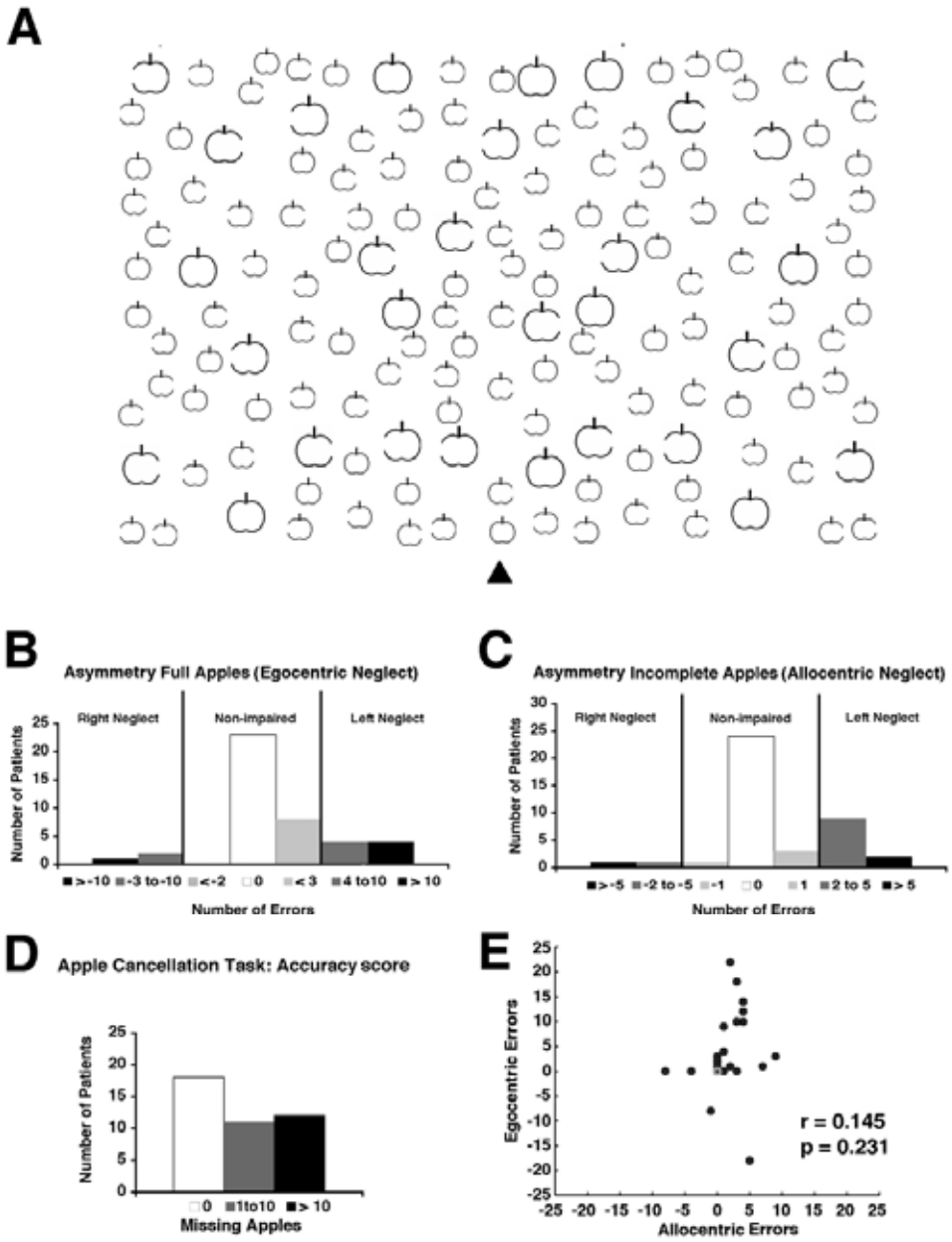

Figure 1. The Apple cancellation task and behavioural results. (**A**) Copy of the page with apples used in the Apple cancellation task. In this test patients are asked to cross all full apples. Egocentric neglect is then measured by whether patients miss targets (full apples) predominantly on one side of the page and allocentric neglect is measured by whether patients make false positive responses by cancelling predominantly left or right distracters i.e. an incomplete apples (for full details and scoring see Methods section). Patients' performance on the Apple cancellations task: (**B**) asymmetry score for full apples used as criterion of egocentric neglect, (**C**) asymmetry score for incomplete apples used as criterion of allocentric neglect and (**D**) accuracy score. (**E**) Scatterplot of patients' egocentric neglect errors against patients' allocentric neglect errors on the Apple cancellation task. There was no significant correlation between allocentric and egocentric neglect scores. Please note that the middle grey dot corresponds to results for non-impaired patients.

RESULTS

Figure 1 shows the behavioural performance of all patients on the Apple Cancellation Task (for full neuropsychological data of the patient group see Supplementary Table 1, Appendix 1). Out of the 41 tested patients, 11 showed left and 2 right allocentric neglect, and 8 patients showed left and 2 right egocentric neglect, assessed relative to control performance. Six patients showed both left egocentric and allocentric neglect, though the severity of impairment varied - with 3 patients having predominantly left egocentric neglect and 3 equal impairments for both types of deficit. One patient showed left allocentric and right egocentric neglect, with equal degrees of severity (see also Riddoch, Humphreys, Luckhurst, Burroughs, & Bateman, 1995). Similarly to previous reports, patients in our study predominantly suffered from unilateral left deficits (Fig. 1B and C). Therefore we restricted further neuroimaging analyses to left unilateral neglect but we used both left and right asymmetry scores for allocentric and egocentric neglect in all statistical models (see Methods for details). As some brain regions may contribute to both left and right deficits this approach was used to avoid biasing the results based on a priori assumptions (e.g. pre-selecting patients based on their anatomical lesions or behavioural scores).

Note that in the following analyses we used continuous scores for both types of neglect. This increased the sensitivity of these measures by accounting for the severity of the symptoms and not just for their categorical presence. Using these continuous scores we could test for correlations between the severity of allocentric and egocentric neglect. Interestingly, there was no significant correlation between these two types of neglect (Fig. 1E; $r=0.145$ at $p=0.231$), supporting a dissociative account of the syndrome (see also Hillis et al., 2005).

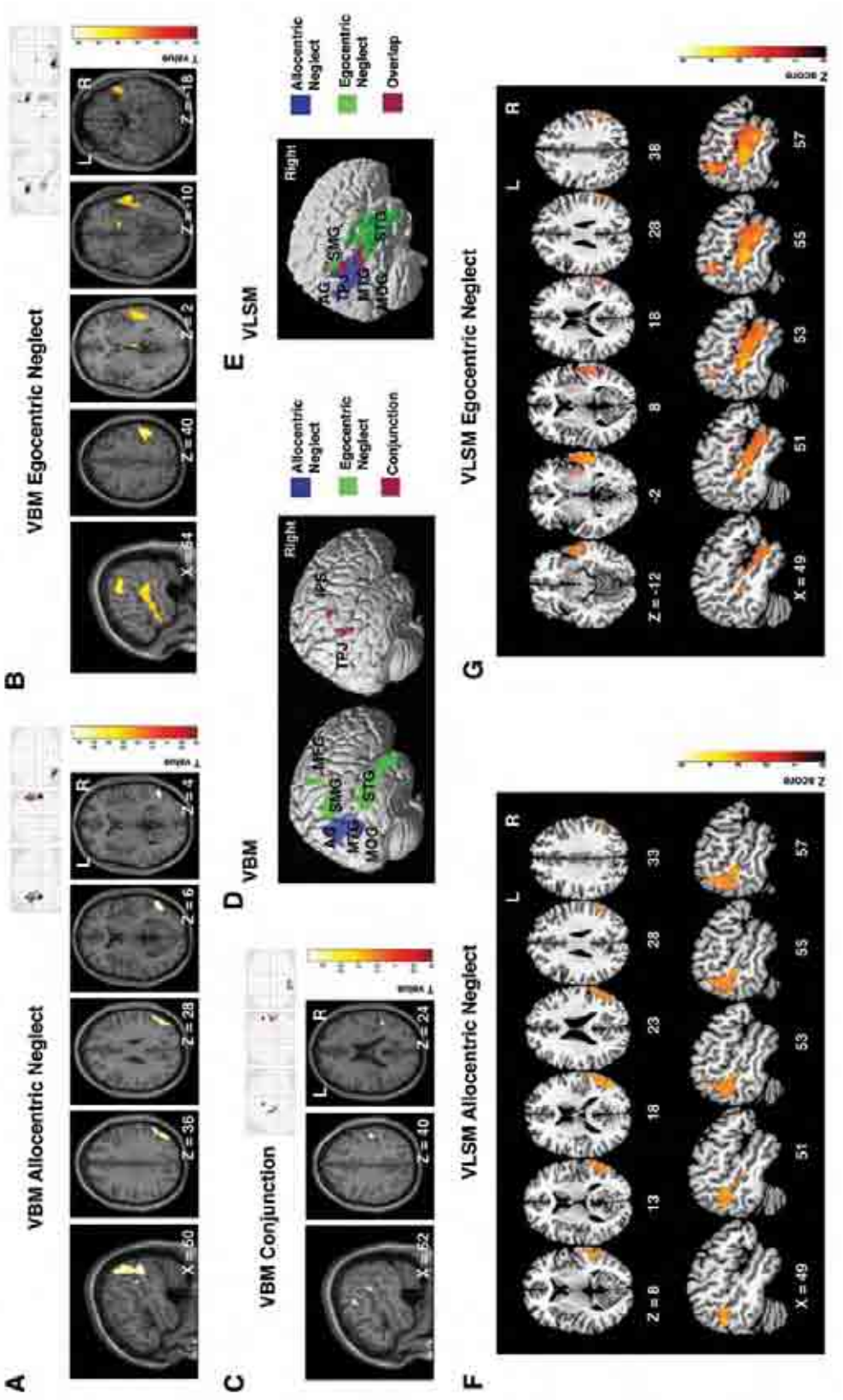

Figure 2. Voxel-wise statistical analysis of grey matter damage: allocentric versus egocentric neglect. Both VBM (**A**, **B**) and VLSM (**F, G**) indicated a striking anterior-posterior dissociation between grey matter substrates of left allocentric and left egocentric neglect. (**C**)

VBM-based conjunction analysis also revealed that damage within right IPS and right TPJ was associated with both left allocentric and left egocentric errors. (**D**) VBM and (**E**) VLSM results indicating both distinctions and commonalities between the grey matter substrates of left allocentric and left egocentric neglect displayed on brain render. Please note that in **A**, **B** and **C** the lesioned areas are coloured according to the significance level in the VBM analysis, where brighter colour means higher t-value. In **F** and **G** statistical maps are displayed after applying a statistical threshold of $P<0.05$, FDR corrected, and are coloured according to the significance level where brighter colour means higher z-score. MNI coordinates of transverse and sagittal sections are given. AG, angular gyrus; IPS, intraparietal sulcus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; SMG, supramarginal gyrus; STG, superior temporal gyrus; TPJ, temporal-parietal junction.

Grey matter: Allocentric versus egocentric neglect

We used two different statistical methods (parametric and non-parametric) to co-vary out allocentric and egocentric components of visual neglect in our lesion analyses, providing a novel comparison of the two approaches. Specifically, using a VBM approach we found that lesions in the right hemisphere within angular, middle temporal (partly extending into inferior temporal), middle occipital gyri and the posterior superior temporal sulcus resulted in left allocentric neglect (Figure 2A and D; see Table 1 for peak MNI coordinates). In contrast damage within the right middle frontal, postcentral, supramarginal, anterior and central superior temporal gyri and the insula (Fig. 2B and D; see Table 1 for peak MNI coordinates) was associated with egocentric errors on the left side of the page. In addition, we found associations between egocentric but not allcoentric neglect and lesioned voxels within sub-cortical structures (Fig. 2B) including the pulvinar and basal ganglia.

Importantly, the VBM approach also allowed us to test for substrates that are common for both types of neglect. The VBM conjunction analysis revealed that damage within right anterior intraparietal sulcus (IPS) and right temporo-parietal junction (TPJ) was associated with both left allocentric and left egocentric errors on the Apple Cancellation Task (Fig. 2C and D; see Table 1 for peak MNI coordinates).

Similarly to the VBM results, our VLSM analysis demonstrated that lesions in the right hemisphere within the angular gyrus (z = 3.49; peak MNI coordinates: 56, -49, 32), the middle temporal gyrus extending into superior temporal sulcus (z = 3.89; peak MNI coordinates: 50, -48, 18), and the middle occipital gyrus (z = 3.07; peak MNI coordinates: 40, -77, 32) resulted in left allocentric neglect (Figure 2F and E). Furthermore, the VLSM analysis linked damage within the right supramarginal gyrus (z = 3.62; peak MNI coordinates: 54, -42, 37), the right anterior and central superior temporal gyrus (z = 3.43; peak MNI coordinates: 54, -27, 2) and the right insula (z = 2.72; MNI peak coordinates: 39, -15, 1) with egocentric errors on the left side of the page (Fig. 2E and G). In addition, we found associations between egocentric but not allocentric neglect and lesioned voxels within the right basal ganglia (z = 2.89; peak MNI coordinates: 20, 9, -10). Finally, we found that, similarly to the VBM conjunction analysis, the VLSM statistical maps of lesion distribution in allocentric and egocentric neglect overlapped within the TPJ, the posterior IPS and also within the border between the middle and superior temporal gyri (Fig. 2E).

In summary, our VBM analyses converge with non-parametric lesion symptom mapping (VLSM) in demonstrating both common and distinct sets of grey matter lesions linked to the two symptoms of neglect. Importantly, both VBM, based on general linear modelling, and non-parametric lesion-symptom mapping (VLSM), demonstrated a striking dissociation between egocentric and allocentric neglect: allocentric neglect was reliably associated with more posterior grey matter damage, while egocentric neglect was linked to more anterior grey matter damage as well as to lesions within subcortical structures.

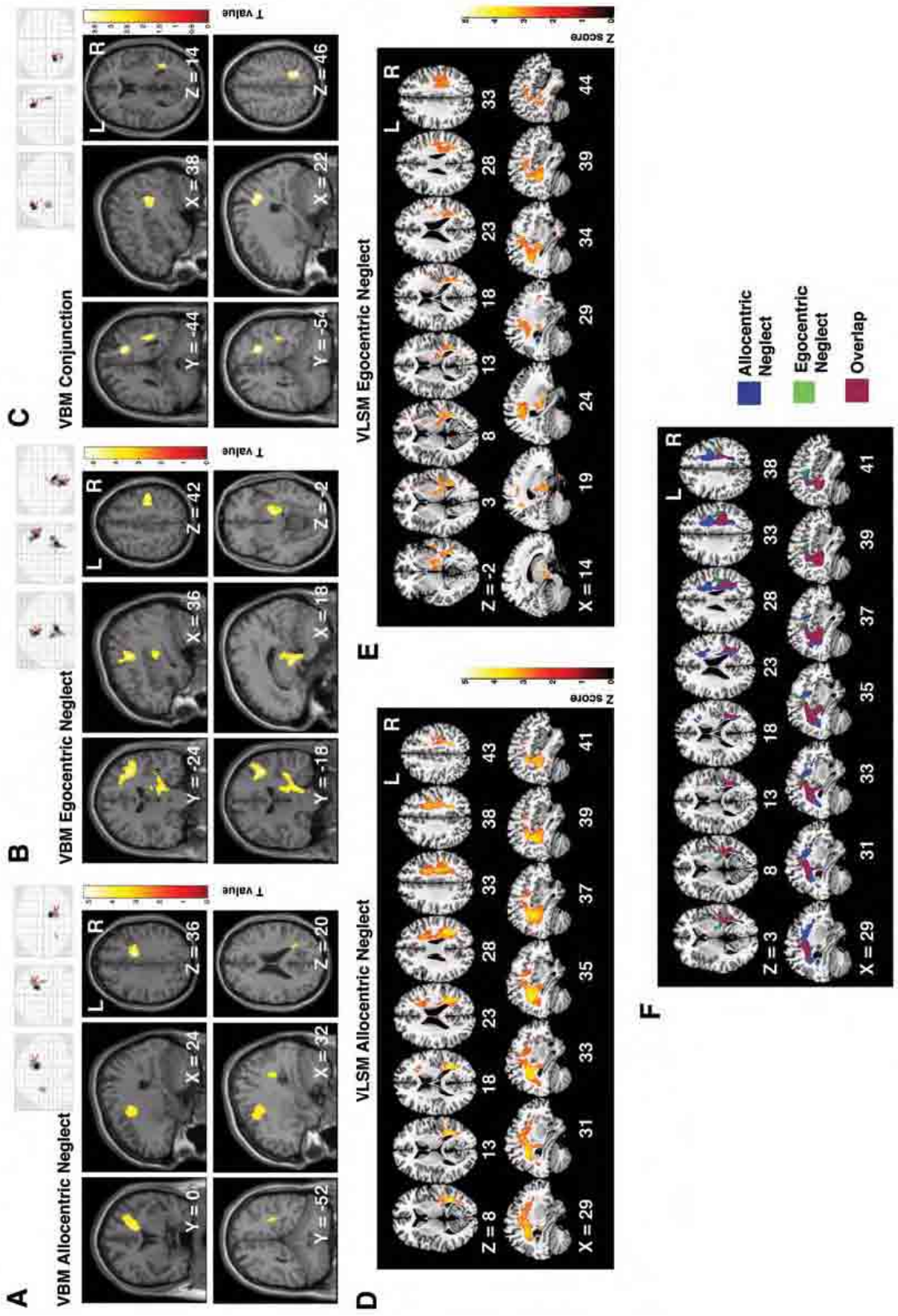

Figure 3. Voxel-wise statistical analysis of white matter damage: allocentric versus egocentric neglect. VBM results showing voxels corresponding to white matter damage in (**A**)

left allocentric, (**B**) left egocentric and (**C**) both forms of neglect (conjunction analysis). Please note that in **A**, **B** and **C** the lesioned areas are coloured according to the significance level in the VBM analysis, where brighter colour means higher t-value. The results of non-parametric analysis of white matter lesions (VSLM) in (**D**) left allocentric, (**E**) left egocentric neglect. Please note that in **D** and **E** statistical maps are displayed after applying a statistical threshold of $P<0.05$, FDR corrected and are coloured according to the significance level, where brighter colour means higher z-score. **(F)** VLSM statistical maps of lesion distribution in allocentric and egocentric neglect showed significant overlap within the same white matter pathways. MNI coordinates of coronal, sagittal and transverse sections are given.

White matter: Allocentric versus egocentric neglect

Similar to our assessments of grey matter damage we used converging statistical and imaging methods to analyse white matter damage, co-varying out allocentric and egocentric components of visual neglect (Fig. 3 and 4, Table 2 and Table 3). Note that, by using T1-contrast images alone, it is difficult to accurately depict the location of damaged voxels within specific white matter tracts. Therefore, one reason for using DTI was to provide a more precise localization of the white matter lesions within a specific pathway. This enabled us to generate qualitative evaluations of colour-coded orientation maps, generated directly based on diffusion tensor vector data that visualize specific pathways (Fig. 4A and C). The results of the statistical analyses (below) were then verified against the individual colour-coded orientation maps.

The neuronal correlates of allocentric and egocentric neglect based on VBM analyses of segmented white matter indicated that the two neglect symptoms were linked to damage within common white matter pathways (Fig. 3A and B; see Table 2 for peak MNI coordinates). Similarly, the non-parametric mapping (VLSM) of white matter lesions of neglect symptoms also showed a clear commonality between the white matter substrates of allocentric and egocentric neglect (Fig. 3D and E). Specifically, white matter lesions consistent with damage within long association and projection pathways including the right SLF and SFO (allocentric - $z = 3.89$, peak MNI coordinates: 24, 0, 36 and $z = 4.03$, peak MNI

coordinates 35, -39, 27; egocentric - z = 3.89; peak MNI coordinates: 22, -32, 49), the right IFO and ILF (allocentric - z= 3.84, peak MNI coordinates: 35, -48, 11; egocentric -z = 3.72; peak MNI coordinates: 36, -61, 21), and right thalamic radiation and right corona radiata (allocentric - z score = 3.71; peak MNI coordinates: 24, -8, 40; egocentric - z score = 3.55; peak MNI coordinates: 35, -26, 3), were associated with both sets of symptoms.

To further investigate the common white matter lesions across the two neglect symptoms, we used conjunction analysis. VBM-based conjunction analysis of segmented white matter lesions from the T1 images showed that damage within regions that seem to be a part of the right posterior SLF, posterior IFOF, posterior ILF, superior corona radiata and superior and posterior thalamic radiations was associated with both allocentric and egocentric neglect (Fig. 3C; Table 2). Furthermore, we found that, similarly to the VBM conjunction analysis, the VLSM statistical maps of the lesion distribution in allocentric and egocentric neglect showed significant overlap within the same white matter pathways (Fig. 3F).

Finally, the conjunction analysis based on the DTI data from a subset of patients showed a decrease in fractional anisotropy in the regions of right white matter that include the following pathways: ILF, IFOF, SLF, SFO, superior and posterior thalamic radiation and anterior and superior corona radiata (Fig. 4E; Table 3). These results were strikingly similar to the findings derived from the segmented white matter using T1 images. Note, however, that the DTI-based analyses showed higher sensitivity to white matter damage when compared to the T1 analyses, despite being based on a smaller number of patients. This suggests that DTI indices such as fractional anisotropy (FA) maybe a more sensitive way in measuring changes in white matter integrity that are associated with abnormal cognitive function i.e., DTI allows to identify even small changes in white matter integrity outside lesion sites detectable by high resolution T1-weighted imaging. The T1- and DTI-based conjunction analyses did not

converge with respect to differential white matter damage within the frontal lobe. The cause of these discrepancies is unclear - it may be due to the differences in imaging methods itself, or to differences between the subset of patients with acquired DTI compared to the whole group.

Importantly, the results from VBM, VLSM and DTI analyses also indicated some dissociations in white matter damage between the two types of neglect. Both T1 based approaches suggest that egocentric neglect involves damage to white matter surrounding the thalamic and basal ganglia nuclei (Fig. 3B,E and 4D). This extends the grey matter results that suggest involvement of pulvinar and basal ganglia in egocentric neglect. Moreover, the DTI and VLSM results indicate that allocentric neglect is associated with damage to more posterior white matter in superior parts of the occipital cortex (Fig. 3F and 4B), which again extends the grey matter results suggesting that overall allocentric neglect is associated with more posterior lesions.

In summary, both of the T1 based approaches we used (VBM and VLSM) converge with the DTI based analyses in demonstrating common white matter lesions across the two neglect symptoms. In particular, lesions within white matter regions that suggested damage within long association pathways including the ILF, the IFOF and the SLF, were linked to both types of deficits.

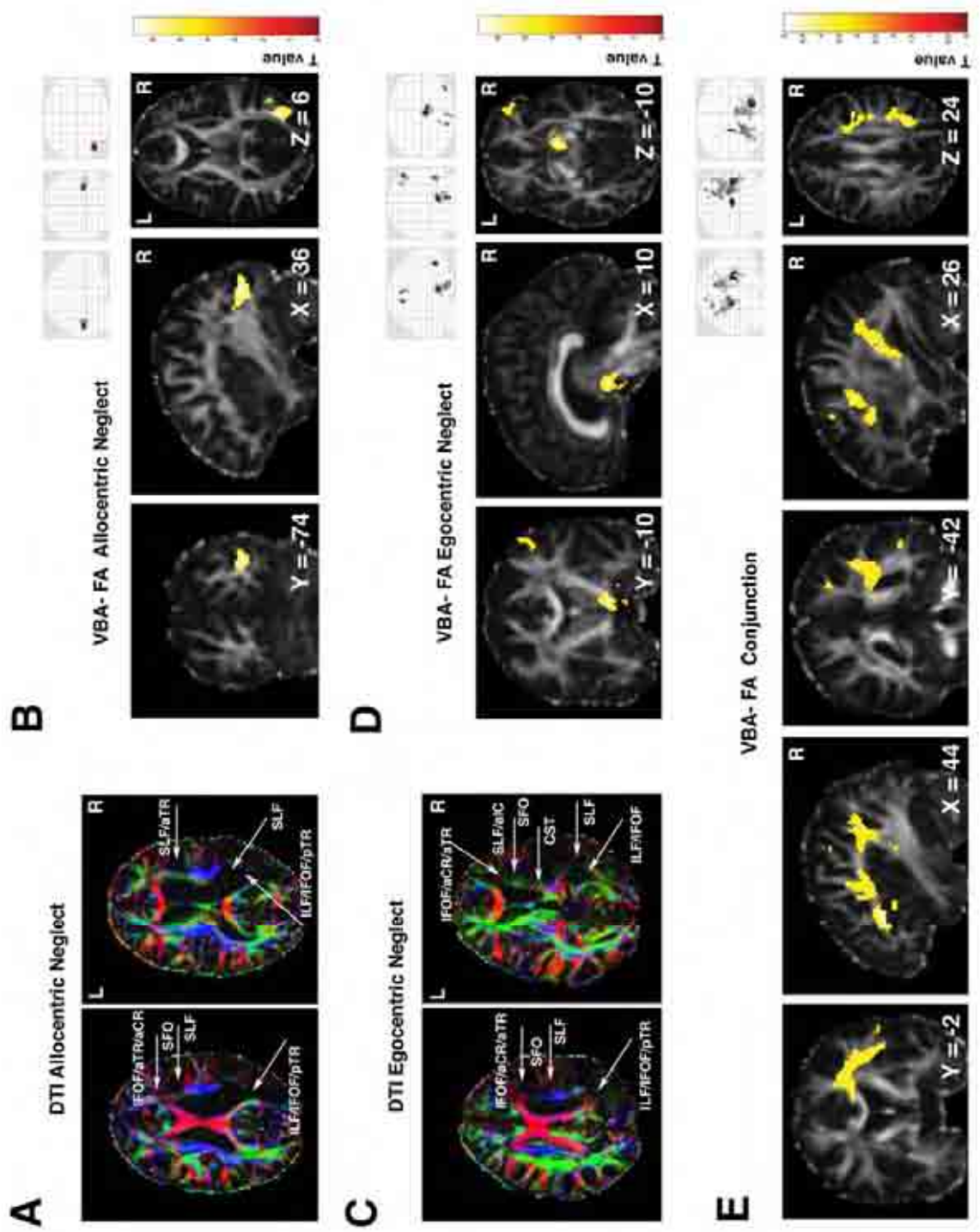

Figure 4. Changes in fractional anisotropy: allocentric versus egocentric neglect. Examples of colour-coded orientation maps showing damage within specific white matter pathways in patient with (**A**) left allocentric and (**C**) left egocentric neglect. Voxel-wise statistical analysis of white matter integrity based on fractional anisotropy in (**B**) left allocentric, (**D**) left egocentric and (**E**) both forms of neglect (conjunction analysis). Please note that similarly to VBM and VLSM analyses of white matter lesions (Fig.3) the damaged areas in both forms of neglect where located within the same white matter pathways. MNI coordinates of coronal, sagittal and transverse sections are given. aCR, anterior corona radiata; aIC, anterior limb of

internal capsule; aTR, anterior thalamic radiation; CST, corticospinal tract IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; pTR, posterior thalamic radiation; SFO, superior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus.

DISCUSSION

Cortical lesions

Here, we examined how damage to grey matter and sub-cortical white matter tracts affect two separate neglect symptoms: egocentric (misses on the left side of the page) and allocentric errors (false alarms to distractors with a left-side gap) in a group of chronic neurological patients. This is in contrast to prior studies, which have examined the neuroanatomical bases of acute visual neglect without differentiating the grey and white matter substrates. We demonstrated both common and distinct sets of lesions linked to the two symptoms of neglect. Most strikingly, we found that there were contrasting regions of cortical damage linked to egocentric and allocentric errors, with allocentric errors associated with more posterior damage (posterior superior temporal sulcus, angular, middle temporal/inferior temporal and middle occipital gyri) than egocentric errors (middle frontal, postcentral, supramarginal and superior temporal gyri as well as the insula). These distinct sites of cortical damage incorporate brain regions contrasted in prior studies of the lesion-symptom mapping in neglect. For example, the analyses reported by Karnath and colleagues (Karnath et al., 2004; Karnath et al., 2002) highlight the association between neglect and relatively anterior cortical regions including the mSTG, the insula and the pre- and postcentral gyri as well as subcortical structures such as putamen, caudate and pulvinar. In our analysis, egocentric neglect was linked to lesions to STG, the supramarginal gyrus, the postcentral gyrus, middle frontal gyrus and insula as well as lesions within basal ganglia and pulvinar. Verdon et al. (2010) also reported that deficits in visuo-motor exploration of egocentric space

was associated with relatively anterior lesions, including damage to dorsolateral prefrontal cortex.

In contrast to these data highlighting relatively anterior lesions, the analyses reported by Mort et al. (2003) stressed that damage to the angular gyrus and the medial temporal lobe/parahippocampus was linked to neglect. We found more specifically that damage to these regions was associated with allocentric neglect. Our data indicate that discrepancies between prior studies may reflect the heterogeneous nature of the neglect symptoms. Karnath and colleagues (Karnath et al., 2004; Karnath et al., 2002) have tended to measure neglect using tasks that require exploration through multiple separate objects, similar to our measure of egocentric neglect. In contrast, Mort et al. (2003) employed as a part of cognitive assessment, line bisection to measure neglect, a task which may be performed by spreading attention across each target line – this would make the task similar to our measure of allocentric neglect (though see Verdon et al., 2010 for a different view). In addition our results are in line with the findings of Rorden et al. (2006) and Verdon et al. (2010), who reported that poor performance on line bisection was associated with posterior brain lesions additional to those found in patients showing neglect only on cancellation and exploration tasks (Rorden et al., 2006; Verdon et al., 2010). Also like Verdon et al. (2010) we link spatial impairments in attending in allocentric space to deficits impinging on medial and inferior occipital-temporal cortex. In sum we suggest that different aspects of neglect are associated with these contrasting lesion sites, with the variations in neglect contributing to the discrepancies in previous findings. Furthermore, our combined analyses of the grey and white matter lesions provide a novel contrast between symptom specific-grey matter damage and symptom general-white matter damage.

Sub-cortical white matter lesions

In addition to the distinct sites of grey matter damage, we found common white matter lesions across the two neglect symptoms. In particular, lesions within white matter regions suggesting damage within long association pathways including the ILF, the IFOF and the SLF, were linked to both measures. These white matter structures may be critical for aligning interactions between neural regions that compete in different ways to select target objects (e.g., connecting between maps which compete to represent different visual features in particular locations respectively in relation to the participant's body and in relation to the objects they are part of (Heinke and Humphreys, 2003). As a consequence, damage to the connecting white matter pathways leads to both egocentric and allocentric neglect. Doricchi and Bartolomeo (Bartolomeo et al., 2007; Doricchi et al., 2008; Doricchi and Tomaiuolo, 2003) used data on white matter deficits associated with neglect to propose that neglect should be considered as a disconnection syndrome. However, while cortical and sub-cortical connections are undoubtedly damaged in the disorder, our results indicate that a disconnection account would miss the critical distinction that exists between allocentric and egocentric forms of deficit, which are associated with distinct cortical sites (see also Verdon et al., 2010). Lesions to white matter tracts will mean that the different spatial representations may fail to be transmitted to response systems, but the cortical substrates of the representations also appear critical.

In a recent study Karnath et al. examined grey matter versus white matter predictors of egocentric (spatial) neglect (Karnath et al., 2009) based on a re-analysis of previous data from this group (Karnath et al., 2004). Karnath et al. (2009) combined a voxel-wise lesion-symptom mapping analysis of manually drawn lesions from either MRI or CT scans collected at an acute stage of stroke with a probabilistic white matter atlas (the Jülich atlas). The results

showed that overall grey matter lesions, particularly within superior temporal, inferior parietal, inferior frontal and insular cortices and sub-cortical structures (such as the caudate and putamen) were stronger predictors of spatial neglect as compared to white matter lesions within the SLF, IFOF and SFO. In contrast to these findings our VBM analyses suggest that both grey and white matter lesions are strongly associated with neglect symptoms. The stronger association between white matter damage and neglect symptoms in our study may be explained by a greater sensitivity of our analyses including DTI and a secondary white matter degeneration of axonal structures present in chronic but not acute patients[7].

Functional accounts of neglect

These data, plus also those emerging from a number of recent neuroimaging studies (Hillis et al., 2005; Marsh and Hillis, 2008; Rorden et al., 2006; Verdon et al., 2010), strongly indicate that visual neglect should not be considered to be a unitary syndrome; rather there can be a number of functionally distinct deficits, subserved by different brain regions, which can lead to contrasting spatial biases in visual selection. In this case, the neurological data constrain functional interpretations of the deficit.

We can consider at least two functional accounts of these results. One is that the contrasting cortical regions support distinct spatial representations of the visual world (Humphreys, 1998). Representations of multiple separate objects are required to support spatial exploration across the page in cancellation tasks, and asymmetrical lesions of these representations may result in egocentric neglect. This would link the supramarginal and postcentral gyri and superior temporal gyrus to representing the locations of multiple separate objects with respect to the patient (a 'between-object' spatial representation; Humphreys,

[7] One potential weakness with the present approach is that the analysis of the grey matter was based on T1 weighted images (see footnote 6 for further comment).

1998). In contrast, the angular gyrus, medial temporal lobe and middle occipital gyrus are involved in representing the spatial locations within objects. An asymmetrical lesion to these representations will lead to allocentric (within-object) neglect.

Alternatively, these different neural regions may support the allocation of attention to the contrasting spatial representations held in other areas, or the regions may support processes that read-in visual information (for egocentric neglect) or that read-out information (for allocentric neglect) from neural networks involved in selecting between stimuli that compete for object recognition. In the computational model of Heinke and Humphreys (2003), for example, visual information is fed-into a selection network where separate objects compete for entry into a focus-of-attention, which itself gates access to stored object knowledge. Selected objects are registered in a location map, which reflects the salience of stimuli in the visual field (SAIM, selective attention for identification model; Figure 5). Heinke and Humphreys demonstrated that damage affecting the visual information coming into one side of the competition network led to egocentric neglect, with there being poor recovery of stimuli on one side of retinally-defined space. In contrast, damage affecting the output from the selection network coming into one side of the focus of led to allocentric neglect, with the contralesional parts of objects being neglected irrespective of their lateral position in the field. From the current data, input into the selection network would be mediated by regions including the supramarginal, the post-central and the superior temporal gyrus; access into the focus of attention would operate through the angular gyrus and more medial occipito-temporal cortex. Interestingly, in a recent model-based analysis of fMRI data from human search, Mavritsaki, Allen & Humphreys (Mavritsaki et al., 2010) have argued for an association between activity in a saliency map in their model and activation of the right temporo-parietal junction (TPJ) in humans. Spatially-specific damage to the location map in

SAIM would lead to poor representation of both whole stimuli on the contralesional side, and also contralesional parts of stimuli, if this location map feeds-back activity to influence activation in the focus of attention and the selection network (see Mavritsaki et al., 2009). This would be consistent with our finding that the right TPJ is associated with both allo- and egocentric neglect.

Alongside the cortical deficits, SAIM may also be able to account for the data from damage to white matter tracts. One proposal stresses neuro-anatomical proximity. For example, within the model there will be close 'anatomical' overlap between the tracts that lead from the selection network and the focus of attention into the location map. As a consequence, damage to brain regions where those tracts link to the location map will generate both allocentric and egocentric neglect, since there will be problems in registering both objects on one side of egocentric space (connections from the selection network) and the elements on one side of each selected object (connections from the focus of attention). In addition, top-down projections from higher-level recognition systems in the model (the knowledge network) carry information about both the location of the object and the locations of elements within objects. Consequently, damage to these projections may generate both profiles of neglect.

A somewhat different way to think about the functional deficits linked to our lesion analysis is that the impairments reflect unilateral problems in attending to local and global spatial representations. For example, the egocentric problems we have identified could be linked to poor attention to one side of a global spatial representation (the positions of the separate objects on the page), while allocentric deficits could stem from impaired attention to the contra-lesional side of local spatial representations (the locations of the gaps on each object). Arguments for a critical role for impairments in global spatial representations in the

neglect syndrome have been made previously. Halligan and Marshall (Halligan and Marshall, 1994b) proposed that neglect emerges from two deficits – an ipsi-lesional bias in attention coupled to an impaired global spatial representation. These authors argued that, due to these combined problems, patients attend to local areas of space on the ipsi-lesional side and fail to re-orient contra-lesionally. This proposal could account for the symptoms of egocentric neglect we have reported, but not for the allocentric deficits in attending to parts within objects. In addition, poor attention to local spatial areas has tended to be associated with left hemisphere rather than right hemisphere damage (Delis et al., 1983), whereas our data highlight a right hemisphere association with allocentric deficits. More detailed studies also suggest that allocentric deficits are unlikely to be fully accounted for in terms of unilateral impairments to local spatial representations. Consider the patient of Humphreys and Riddoch (1994), who presented with left allocentric (e.g., making errors on the left side of individual words) but right egocentric neglect (missing whole words on the right of the page). This patient continued to display the same allocentric problems when letters were expanded across the page so that a single word then covered the same area as sets of smaller, individual words in previous tests. Thus, the patient read the enlarged letters in areas on the right of the page where he had previously omitted whole words, but he made errors to letters on the left of the enlarged words in regions where previously he detected smaller whole words. In such a case, the size of the spatial area covered by the stimuli seems less critical than whether the patient is attempting to scan from one independent object to another (where he had a deficit on the right side of space) or is assimilating all the elements together as part of a single perceptual object (where he had a deficit on the left side of space). Nevertheless, the argument about local and global representations is itself compatible with models such as SAIM. Within SAIM, competition within the selection network operates at a global level of spatial

representation, between separate objects in the visual field. In contrast, the assimilation of elements into the focus of attention operates at a more local level of the individual selected object. The model provides a framework for understanding the inter-relation between global and then more local selection processes.

Our argument for posterior occipital-temporo-parietal sites being important for allocentric processing contradicts Vallar et al. (Vallar et al., 2003) and Medina et al. (Medina et al., 2009), who associated allocentric neglect with ventral stream lesions and egocentric neglect with dorsal stream lesions. Partly this may reflect differences in test material, with some studies using items with clearer lexico-semantic representations than our figures, and these lexico-semantic stimuli may recruit more ventral cortex. Previously (Karnath, 2001) proposed that the superior temporal cortex in humans, which receives inputs from both dorsal and ventral visual stream, should be considered as an interface between allocentric and egocentric visual attention systems. We found that lesions within superior temporal cortex were associated with both forms of neglect, though with there remaining an anterior-posterior sub-division consistent with the general anterior-posterior distinction between egocentric and allocentric deficits (posterior STS/allocentric; anterior and central STG/egocentric neglect). Nevertheless our data fit with the superior temporal cortex being an important convergence region, bringing together different forms of spatial representation. Our results suggest however that the convergence is not simply from ventral and dorsal pathways but may include bringing together different spatial representations within a parieto-frontal network. We note too that Medina et al. (2009) found an association between damage within STG and egocentric neglect, while their previous study showed association between STG and allocentric neglect (Hillis et al., 2005). Our finer-grained analysis suggests that both types of neglect can arise after damage to the superior temporal cortex, though differences may

emerge when the lesion is sufficiently small to selectively affect more anterior or posterior sections.

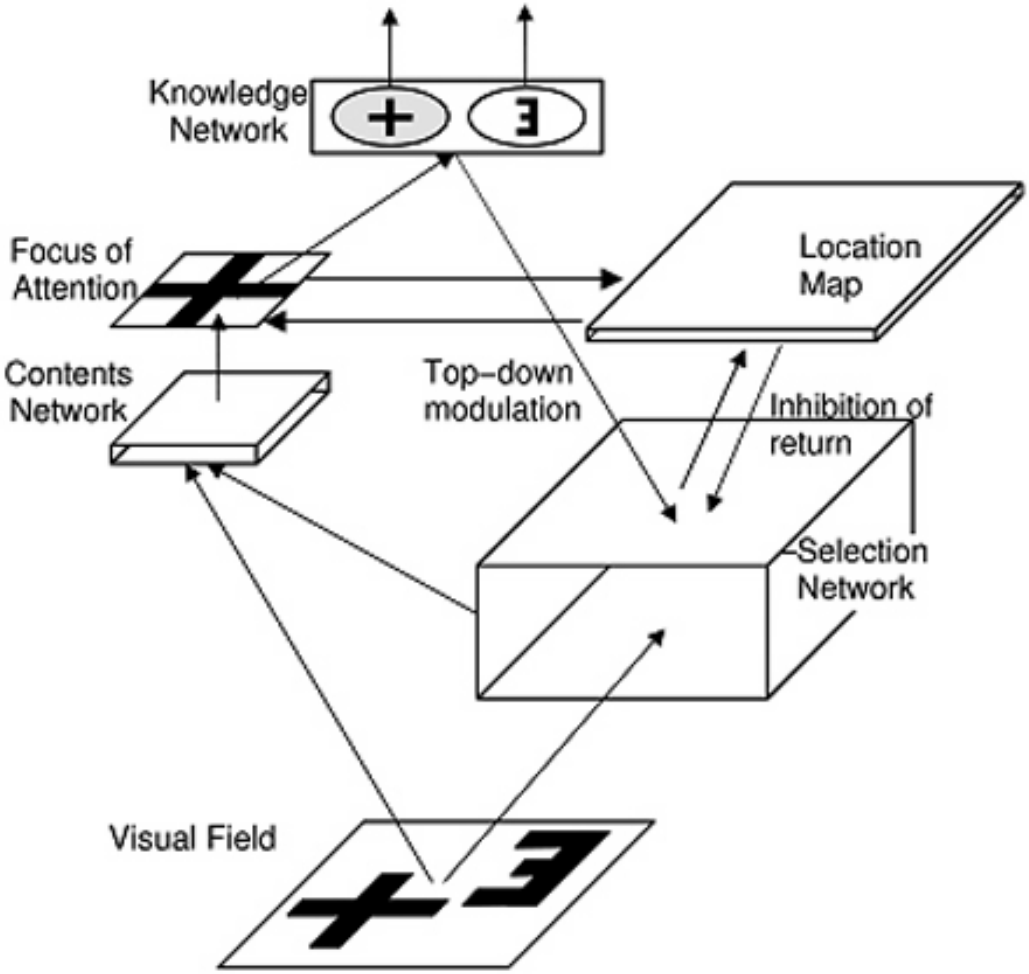

Figure 5. The SAIM model of visual selection (Heinke and Humphreys, 2003). Copyright 2003 by the American Psychological Association. Adapted with permission of D. Heinke and G.W. Humphreys

Conclusions

We conclude that our data point to distinct cortical regions controlling attention (i) across space (using an egocentric frame of reference) and (ii) within objects (using an allocentric frame of reference), along with common cortical regions and white matter

pathways that support interactions across the different cortical regions. We suggest that egocentric codes computed in a fronto-parieto-temporal network and integrated with allocentric codes computed in a parieto-temporal-occipital network, converge within IPS, TPJ and superior temporal cortex and share common white matter pathways. These distinct regions can be linked to different functional modules within computational models of human visual selection.

Table 1. Grey matter substrates: left allocentric versus left egocentric neglect: results from VBM analysis**.**

Contrast	cluster level		voxel level	Coordinates			Brain Structure
	P_{corr}	Size	Z-score	X	Y	Z_c	
Allocentric errors:	0.000	830	3.73	**54**	**-58**	**6**	right MTG/ITG* and MOG,
(p<0.001 uncorr.)			3.60	50	-58	44	right posterior STS,
			3.57	50	-62	30	right angular gyrus
Egocentric errors:	0.000	596	5.04	**52**	**-32**	**40**	right SMG
(p<0.001 uncorr.)	0.000	980	3.71	**48**	**-24**	**-8**	right STG
			3.68	54	-30	2	right insula
	0.034	80	4.18	**44**	**-8**	**62**	right MFG
	0.140	58	4.03	**4**	**-22**	**-2**	right pulvinar
	0.881	51	3.50	**16**	**8**	**-10**	right basal ganglia
Conjunction:	0.924	73	3.11	**50**	**-38**	**18**	right TPJ
(p<0.005 uncorr.)	1.000	46	3.07	**50**	**-22**	**40**	right IPS

AG, angular gyrus; IPS, intraparietal sulcus; ITG, inferior temporal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; SMG, supramarginal gyrus; STG, superior temporal gyrus; STS, superior temporal sulcus; TPJ, temporal-parietal junction;
*lesion within middle temporal gyrus partly extending into inferior tempral gyrus.

Table 2. White matter substrates: left allocentric versus left egocentric neglect: results from VBM analysis**.**

Contrast	cluster level		voxel level	Coordinates			Brain Structure*
	P_{corr}	Size	Z-score	X	Y	Z	
Allocentric errors:	0.000	691	4.39	**16**	**0**	**36**	right ant. SFO and SLF
(p<0.001 uncorr.)			3.50	32	0	42	right sup. CR and TR
			3.48	28	10	42	
	0.094	76	3.50	**32**	**-52**	**20**	right post. ILF and IFOF
Egocentric errors:	0.000	694	4.50	**42**	**-18**	**42**	right SFO and SLF, sup. CR
(p<0.001 uncorr.)			4.01	34	-14	52	and TR, post. IC and CST,
			3.87	48	-24	48	right post. ILF and IFOF,
	0.000	949	4.45	**22**	**-8**	**-2**	right CST, sup. TR, post. IC
			3.95	36	-24	6	
			3.83	18	-18	-10	
Conjunction:	0.00	266	3.44	**22**	**-54**	**46**	right sup. SLF, CR and TR
(p<0.005 uncorr.)			3.27	20	-44	50	
	0.014	177	3.19	**38**	**-48**	**14**	right post. SLF, ILF, IFOF and TR

ant, anterior; post, posterior; sup, superior; CR, corona radiata; CST, corticospinal tract; IC, internal capsule; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; SFO, superior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus; TR, thalamic radiation; * the location of white matter lesions suggests damage to specific white matter pathways as listed below.

Table 3. White matter substrates: left allocentric versus left egocentric neglect: results from VBA-FA analysis**.**

Contrast	cluster level		voxel level	Coordinates			Brain Structure*
	P_{corr}	Size	Z-score	X	Y	Z	
Allocentric errors:	0.000	212	3.96	**36**	**-74**	**6**	right post. ILF, IFOF and CR
(p<0.001 uncorr.)			3.40	38	-64	6	right post. SLF and ILF
	0.000	56	3.28	**56**	**-64**	**4**	
Egocentric errors:	0.000	373	4.23	**10**	**-4**	**-10**	right ant. and sup. TR,
(p<0.001 uncorr.)			4.13	8	0	-28	right IC and CST
			4.12	10	8	-32	
	0.000	108	4.19	**48**	**42**	**-6**	right ant. IFOF
	0.000	124	4.17	**50**	**-30**	**52**	right ant. SLF and CR,
			3.82	54	-10	50	right sup. TR and CR
			3.47	36	-24	54	
Conjunction:	0.000	1245	3.52	**44**	**16**	**16**	right ant. SFO, SLF, IFOF and CR
(p<0.005 uncorr.)			3.44	16	4	48	
			3.17	40	24	12	
	0.001	966	3.59	**22**	**-28**	**22**	right sup. and post. TR, right post.
			3.26	2	-36	14	SLF, ILF and IFOF
			3.14	38	-46	34	
	0.995	65	3.11	**24**	**-42**	**52**	right sup. CR and TR

All abbreviations as in Table 2

CHAPTER 3:

THE CENTRAL ROLE OF THE TEMPORO-PARIETAL JUNCTION AND THE SUPERIOR LONGITUDINAL FASCICULUS IN SUPPORTING MULTI-ITEM COMPETITION: EVIDENCE FROM LESION-SYMPTON MAPPING OF EXTINCTION[8]

[8] This Chapter is published in *Cortex:* Chechlacz M, Rotshtein P, Hansen PC, Deb S, Riddoch JM, Humphreys GW. The central role of the temporo-parietal junction and the superior longitudinal fasciculus in supporting multi-item competition: evidence from lesion-symptom mapping of extinction. *Cortex* (2012), doi:10.1016/j.cortex.2011.11.008.

ABSTRACT

The present study examined the relations between the lesions linked to visual and tactile extinction, and those related to visual field defects and spatial (egocentric) neglect. Continuous variations in patients' performance were used to assess the link between behavioural scores and integrity of both grey and white matter. We found both common and distinct neural substrates associated with extinction and neglect. Damage to angular and middle occipital gyri, superior temporal sulcus and insula were linked to visual extinction. Lesions involving the supramarginal gyrus, intraparietal sulcus, middle frontal and superior temporal gyri were associated exclusively with spatial[9] neglect. Lesions affecting the temporo-parietal junction (TPJ), the middle temporal region, middle frontal area (BA46) as well as the insula and putamen were linked to both spatial neglect and visual extinction. Analysis of the relations between visual and tactile extinction highlighted the TPJ as the common site for both modalities. These findings suggest that the TPJ plays a general role in identifying salient events in the sensory environment across multiple modalities. Furthermore, white matter analyses pointed to superior longitudinal fasciculus (SLF) as critical for interconnecting components of the visuospatial attention network. We demonstrated that functional disconnections resulting from SLF damage contribute to altered performance on attention tasks measuring not only neglect but also visual and tactile extinction. We propose that the SLF supports interactions between functionally specialized regions involved in attentional control across multiple sensory modalities.

[9] spatial neglect = egocentric neglect; in this chapter I use primarily term spatial neglect for consistency with previous published papers (e.g. Karnath et al., 2003) and consistency with published version of this chapter.

INTRODUCTION

Most common clinical symptoms associated with deficits of spatial attention are associated with the syndrome of unilateral neglect, where patients fail to respond to even single items on the side of space contralateral to the brain lesion (Heilman and Valenstein, 1979). In many cases, however, patients can respond to a single contralesional item but fail to detect this same stimulus when an ipsilateral item is present concurrently. This is the phenomenon of extinction (Bender and Teuber, 1946; Critchley, 1953; Wortis et al., 1948). Extinction can be considered as a disorder of visuospatial attention characterized by a striking bias for ipsilesional item(s) at the expense of contralesional item(s), so the deficit on contralesional items emerges when there is attentional competition from stimuli on the ipsilesional side (see Duncan et al., 1997).

Neuro-anatomical relations between extinction and neglect

Neglect and extinction have been frequently reported together (e.g., Mattingley et al., 1997; Ptak et al., 2002; Rees et al., 2000; Riddoch et al., 2010; Vuilleumier and Rafal, 2000). One view suggests that extinction is a mild type of neglect, part of the neglect syndrome or even a sign of partial recovery from neglect (Karnath, 1988; Rafal, 1994; Robertson and Halligan, 1999). An alternative view argues for a dissociation between these two syndromes (Di Pellegrino and De Renzi, 1995; Liu et al., 1992; Pavlovskaya et al., 2007; Vallar et al., 1994) though see Geeraerts et al., 2005). In support of the clinical dissociation view, recent studies provide evidence for an anatomical dissociation between neglect and extinction (e.g. Karnath et al., 2003; Vallar et al., 1994).

The most common lesion sites associated with the neglect syndrome include the posterior parietal cortex (PPC), inferior parietal lobe (IPL), and the temporo-parietal junction (TPJ; see Leibovitch et al., 1998; Vallar, 2001; Vallar et al., 2003; Vallar and Perani, 1986).

Some studies also suggest that damage within the medial temporal lobe (the parahippocampus; (Mort et al., 2003), the inferior frontal cortex (Husain and Kennard, 1996; Vallar, 2001; Walker et al., 1998) and the mid superior temporal gyrus (STG) can lead to neglect (Karnath, 2001; Karnath et al., 2001).

In contrast to the substantial number of lesion-symptom studies examining the neuronal substrates of neglect in large patient groups, the anatomical substrates of visual extinction have been studied less extensively. Evidence for the neural correlates of extinction come mostly from single case reports and virtual lesion studies (transcranial magnetic stimulation, TMS) in healthy participants, where visual extinction has been linked to disruption to posterior parietal cortex (Battelli et al., 2009; Critchley, 1949; Hilgetag et al., 2001; Pascual-Leone et al., 1994; Rees et al., 2000). However, a small number of reports based on lesion-symptom analyses in groups of stroke patients have associated visual extinction with lesions outside the parietal cortex (Hillis et al., 2006a; Karnath et al., 2003; Ogden, 1985; Ticini et al., 2010; Vallar et al., 1994) – with critical regions including the dorsolateral frontal cortex (Vallar et al., 1994), visual association cortex (Hillis et al., 2006a) and subcortical (basal ganglia) structures (Ogden, 1985; Ticinin et al., 2010; Vallar et al., 1994). The TPJ also seems to be critical to the emergence of extinction. For example, Karnath et al. (2003) reported four patients with ‘pure’ visual extinction (extinction without neglect) with lesions to the TPJ. Similarly Ticni et al., (2010) show that malperfusion of the TPJ is associated with visual extinction in patients with basal ganglia lesions. On the other hand, the TPJ has also been associated with visual neglect (e.g., Chechlacz et al., 2010 [Chapter 2 here]; Leibovitch et al., 1998; Vallar, 2001; Vallar et al., 2003). From this we do not know whether the TPJ plays a common functional role in tests of neglect and extinction, with the magnitude

of the lesion being critical, or whether different functional roles emerge according to the precise lesion site.

Extinction in different modalities

Although extinction has been studied most extensively in the visual modality, it is well documented that effects occur also in other sensory modalities including touch, audition and olfaction (e.g. Bellas et al., 1988a, b; De Renzi et al., 1984; Deouell and Soroker, 2000; Hillis et al., 2006a; Ladavas et al., 2001; Maravita et al., 2000; Vaishnavi et al., 2001). The functional and neuro-anatomical relations between extinction in different modalities are poorly understood. Are there any particular processes and brain regions that, when lesioned, produce modality-specific extinction, and others that generate problems across different modalities? One aim of this study was to examine the neuronal substrates of visual versus tactile extinction (see also Hillis et al., 2006a; Vallar et al., 1994), in an attempt to pull apart the relations between these disorders.

Disconnection syndromes

Rather than associating neglect with a specific cortical site, some researchers have viewed neglect as a disconnection syndrome (Bartolomeo et al., 2007; Doricchi and Tomaiuolo, 2003) resulting from structural disruption of connectivity within attention networks. Specifically, neglect has been associated with damage to the superior longitudinal (SLF; Chechlacz et al., 2010 [Chapter 2 here]; He et al., 2007; Thiebaut de Schotten et al., 2008), the inferior longitudinal (ILF; Bird et al., 2006) and the inferior fronto-occipital fasciculi (IFOF; Chechlacz et al., 2010 [Chapter 2 here]; Riddoch et al., 2010; Urbanski et al., 2008). The role that sub-cortical disconnections may play in visual extinction, and whether there are common or separate white matter disconnections in neglect and extinction, have not been previously examined. This was done here.

Table 4. Patients details: clinical and demographic data

ID	Sex/Age/ Handedness	Aetiology	Time post lesion (year)	Lesion side	VE* uni	VE bilat	ACT** /50	ACT assym	TE*** uni	TE bilat
P1	M/73/R	S	2	B	0	0	50	0	0	0
P2	M/55/R	S	4	B	**11**	**18**	46	2	0	0
P3	M/60/R	S	12	R	0	**6**	47	0	**2**	**6**
P4	M/69/R	S	1	B	**-20**	**-38**	40	**-3**	0	0
P5	M/63/R	S	5	B	**7**	**36**	**22**	**22**	**3**	**8**
P6	F/65/R	CBD	4	B	**9**	**14**	**10**	**10**	0	**5**
P7	M/71/R	S	14	L	0	-1	50	0	0	0
P8	M/67/R	S	1	L	-2	**-18**	48	-2	0	0
P9	M/38/R	CM	12	B	0	**-12**	49	0	0	0
P10	M/70/R	CM	12	B	-1	**10**	50	0	0	**-2**
P11	F/40/R	S	1	B	2	2	50	0	0	0
P12	M/52/R	HSE	15	R	0	2	50	0	0	0
P13	M/66/R	S#	18	B	**10**	**26**	**14**	**14**	1	**5**
P14	F/20/R	PS	20	B	0	**-30**	50	0	0	1
P15	M/85/R	S##	26	B	0	-2	50	0	0	0
P16	F/63/L	S	3	R	**7**	**13**	45	3	0	0
P17	F/47/R	S##	3	B	0	**4**	**6**	**4**	0	1
P18	F/72/R	S#	4	B	**3**	**10**	50	0	**4**	**8**

P19	M/61/R	S	1	R	**6**	**12**	48	0	0	0
P20	M/62/R	CBD	3	R	1	**3**	50	0	**-2**	0
P21	M/61/R	S	5	R	0	1	50	0	0	0
P22	M/56/R	S	1	R	**9**	**33**	48	0	0	**2**
P23	M/71/R	S	2	R	2	-2	48	0	0	0
P24	M/37/R	S	1	R	**5**	**12**	45	0	0	0
P25	M/76/R	S	3	R	**10**	**22**	50	0	0	0
P26	M/69/R	S	4	R	**6**	**32**	**32**	**18**	0	**8**
P27	F/60/R	S	1	L	**-3**	**-12**	44	3	1	0
P28	M/65/R	S	2	R	2	**11**	**32**	**9**	0	1
P29	M/64/R	S	1	R	**10**	**30**	**40**	**10**	0	**6**
P30	M/54/L	CM	10	L	0	**-7**	50	0	0	0
P31	M/77/R	S	1	L	2	0	**25**	**-9**	0	0
P32	M/61/L	S	12	R	**10**	**40**	**40**	**9**	0	0
P33	M/48/R	S	5	R	0	0	50	0	0	0
P34	M/75/R	S	3	L	**-10**	**-12**	36	0	0	0
P35	F/60/R	S#	13	B	1	**12**	47	1	0	0
P36	M/34/R	S	9	L	**-5**	**-35**	50	0	0	0
P37	M/67/L	S#	2	B	2	**25**	45	0	0	**4**
P38	M/72/R	S	4	L	**-4**	**-16**	50	0	-1	**-8**
P39	M/72/R	S	7	R	-2	**19**	50	0	0	0

P40	M/63/R	CBD	3	B	**-5**	**13**	**18**	**-18**	0	**3**
P41	M/53/R	S	3	R	**4**	**30**	47	3	0	**2**
P42	M/73/R	S	8	L	**-7**	**-30**	50	0	0	0
P43	M/73/L	S	8	L	-2	**-13**	44	4	0	0
P44	F/58/R	S##	4	B	0	0	50	0	0	0
P45	M/55/R	HSE	10	B	1	1	50	0	0	0
P46	M/70/R	S	7	R	**4**	**26**	**38**	**12**	0	**4**
P47	F/78/R	S	1	R	0	-2	36	0	0	0
P48	M/60/R	S	1	B	**-6**	**-21**	50	0	0	-1
P49	M/62/R	S	1	B	**-9**	**-11**	**40**	**-5**	0	-1
P50	F/38/R	S	1	L	-1	**-5**	50	0	0	0

ACT = Apple Cancellation task; assym = asymmetry score; B = bilateral; bilat = bilateral asymmetry score; CBD = cortico-basal degeneration; CM = carbon monoxide poisoning; F = female; HSE = herpes simplex encephalitis; M = male; L = left; R= right; PS = perinatal stroke; S = stroke; # = second stroke (time post lesion indicate first diagnosis, patients tested > 9 months post second diagnosis; ## = large posterior cerebral artery bleeds; TE = tactile extinction task; uni = unilateral asymmetry score; VE = visual extinction task; VFD = visual field deficits; *The visual extinction task consists of 24 unilateral left, 24 unilateral right and 48 two item trials. **The maximum achievable score in the Apple Cancellation task is 50. Spatial neglect is determined by whether patients miss targets (complete apples) on the left or right side of the page (asymmetry score calculated based on left- vs. right-side errors). ***The tactile extinction task consists of 4 unilateral left, 4 unilateral right and 8 bilateral trials. **Scores where there is a clinical deficit are highlighted in bold (for details of all tasks and cut-off scores see Methods section).**

The current study

Taking all the above points into account, the current study examined the neuronal substrates of visual extinction along with the neuroanatomical relations between (i) visual extinction and spatial (egocentric) neglect, and (ii) visual and tactile extinction. As well as covering a wider set of symptoms (e.g., tactile as well as visual extinction along with unilateral neglect), the current investigation differs from previous reports in terms of data analysis methods. Our analyses were based on sample of consecutive patients admitted to the Behavioural Brain Sciences (BBS) Centre at Birmingham University with the presence of a variety of neuropsychological phenomena (dysexecutive syndrome, language deficits, apraxia, aspects of the neglect syndrome, alexia) and who were not pre-selected based on clinical or anatomical criteria. This allows us to contrast patients with the symptoms of interest with control patients, without these symptoms. We employed whole brain statistical analyses (voxel-based morphometry VBM; Ashburner and Friston, 2000) in order to look for common structure-function relationships across the whole brain, separately for grey and white matter. Importantly, the analyses controlled for potential confounding factors such as aetiology (stroke, degenerative changes), age-related changes, time since lesion, lesion volume and visual field deficits. In addition in all analyses the behavioural measurements were treated as continuous variables rather than as categorical scores. Lesion-symptom mapping studies of extinction have typically used a binary classification of patients into impaired and non-impaired groups (e.g. Hillis et al., 2006a; Karanah et al., 2003; Ticini et al., 2010; Vallar et al., 1994). One problem with binary classifications is that they might fail to capture relations between the degree of damage and the magnitude of the deficit in patients. Here we use both continuous behavioural scores and continuous anatomical information (Chechlacz et al., 2010 [Chapter 2]; Leff et al., 2009) that allowed us to take into account that

visual extinction is typically not an all-or-none phenomenon and instead reflects the relative competition between contra- and ipsilesional stimuli in different patients.

The results are discussed in relations to the anatomical dissociations between extinction and neglect as well as the functional organization of the interconnected networks underlying visual and tactile spatial attention.

METHODS

Participants

Patients. Fifty patients participated (39 males and 11 females), with ages ranging from 20 to 85 years (mean age 61.2 years). All patients had acquired brain lesions (42 stroke, 3 degenerative changes, 3 carbon monoxide poisoning and 2 encephalitis[10]; see Footnotes at the end of the manuscript), were at a chronic stage (> 9 months post diagnosis) and had no contraindications to MRI scanning. No other exclusion criteria were used. See Table 4 for full clinical and demographic data.

All the patients were recruited from the panel of neuropsychological volunteers established in the Behavioural Brain Sciences Centre at the School of Psychology, University of Birmingham. All patients provided written informed consent in agreement with ethics protocols at the School of Psychology and Birmingham University Imaging Centre (BUIC).

Healthy Controls. For the lesion identification protocol (see below) we acquired T1-weighted images from 100 healthy controls (55 males and 45 females, mean age 54.5 years, range 20-87) with no history of stroke, brain damage or neurological disorders. All the

[10] All patients included in this study were chronic and out of 50 patients, only three suffered from carbon monoxide poisoning and five from degenerative changes (three of these patients also suffered from different forms of unspecified vascular disease causing additional acquired focal brain lesions). Omitting the small number of non-stroke patients from the analyses made little difference to the results. These patients are included in all analyses reported here to maximise power.

controls provided written informed consent in agreement with ethics protocols at the School of Psychology and BUIC.

Cognitive assessment

Visual extinction. In order to measure visual extinction we used a simple computer test presented on a PC running E-Prime software (Psychology Software Tools). The test was based on a single experimental block consisting of 96 randomized trials. There were 48 single item trials (24 left and 24 right) and 48 bilateral trials. In both unilateral and bilateral trials the stimuli were presented on the black background inside white outlines of rectangles positioned in the left and right hemifield. On unilateral trials patients were presented with stimulus consisting of a single white letter (~0.5deg horizontally and vertically) at the centre of either the left or right rectangle (centred 3deg into each field). On bilateral trials two white letters were positioned respectively at the centre of the left and right rectangles. There were 4 possible targets to identify (the letters A, B, C and D). At the beginning of the test participants were instructed "Your task is to fixate on the centre of the screen and to respond to the appearance of the letter(s) by saying the letter(s) you see out loud". Participants were instructed that they might see more than one letter on a given trial. Each trial began with a 200ms presentation of a white fixation cross on the black background at the centre of screen between the white rectangles. This was followed by brief presentation of a unilateral or bilateral stimulus for 200ms after which patients were asked to freely report the letter(s). The maximum achievable score on bilateral trials was 48 and also 48 (24 left plus 24 right) on unilateral trials. We recoded the number of correct bilateral responses as well as number of right and left omissions (errors) on unilateral and bilateral trials.

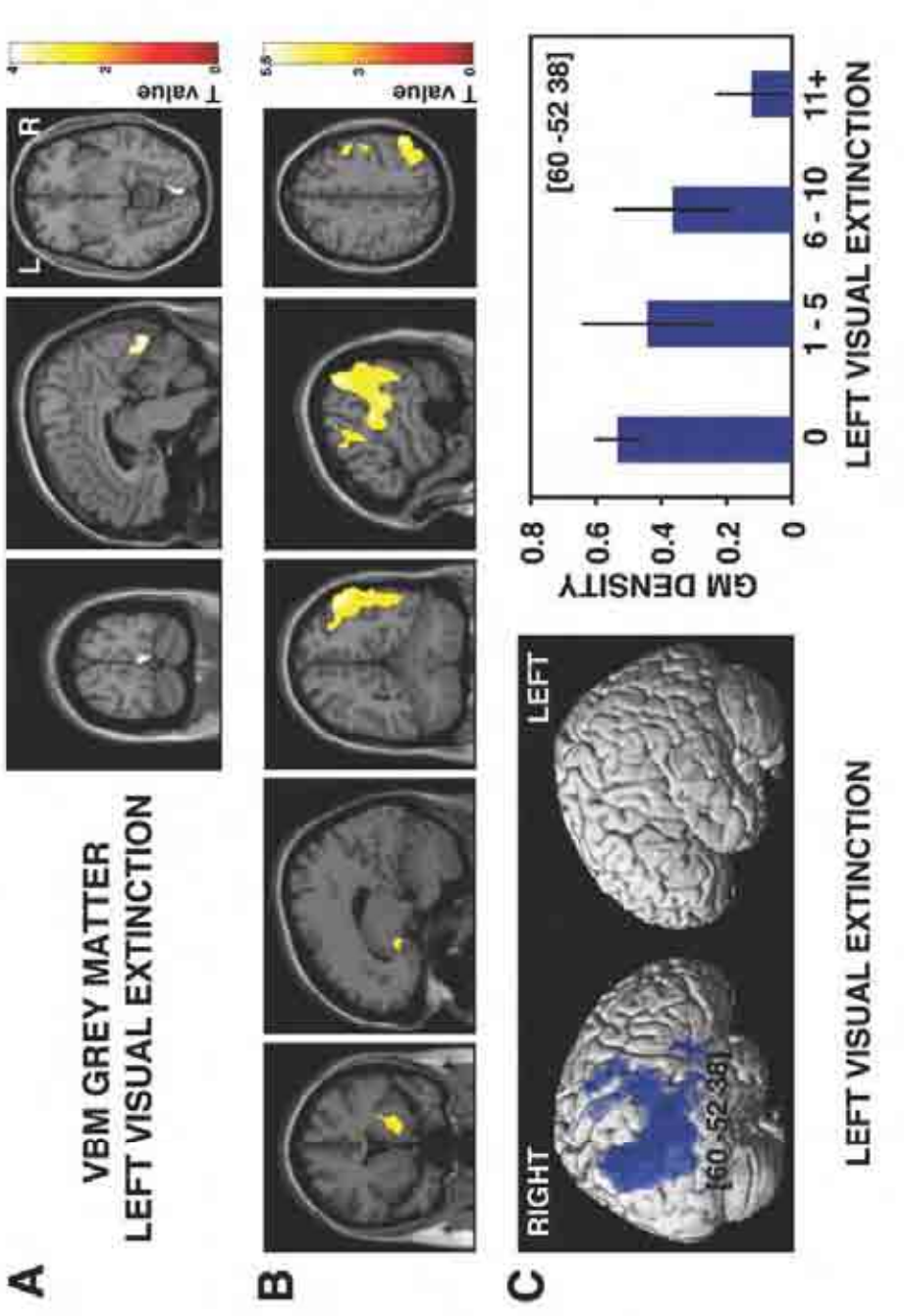

Figure 6. Neuronal substrates of left visual extinction: VBM analysis of grey matter. Results from Analysis 1 depicting **(A)** grey matter substrates contributing to left visual field deficits/visual neglect problems (performance on 1-item/unilateral trials; left unilateral asymmetry score) and **(B)** left visual extinction (left visual extinction index). Please note that in **A** and **B** the lesioned areas are coloured according to the significance level in the VBM analysis, where brighter colour means higher t-value. **(C)** To further illustrate the relationship between grey matter loss and left visual extinction deficits, we first extracted the principal eigenvariate of the voxels within the entire main cluster identified in VBM analysis (cluster with MNI coordinates 60 -52 38 shown on brain render) and plotted against the visual extinction score (left visual extinction index).

Asymmetry scores: Based on left and right omissions we calculated an asymmetry score on the difference in report on left- and right-side items, separately for unilateral and bilateral trials. The performance on unilateral trials gives a measure of a field defect or neglect (unilateral bias).

Extinction index: The difference in the asymmetry score on bilateral versus unilateral trials was assessed, to index any spatially selective drop in response to two stimuli relative to the presentation of one stimulus. This was done separately for both left- and right-side items. To do this we calculated an extinction index i.e. the unilateral asymmetry score multiplied by two minus the bilateral asymmetry score, taking into account the difference in the number of trials.

The extinction index and the asymmetry score for both left- and right-side unilateral items were entered into the statistical models.

Control norms for visual extinction test were assessed based on performance of 10 control participants with no history of neurological diseases and no lesions on MRI scans (5 males and 5 females, age range 62-74). Cut-offs to classify patients as having visual extinction were calculated on the basis of bilateral asymmetry scores (left vs. right-side errors). Control participants made a maximum of two errors on a single side or both sides and therefore the asymmetry scores >2 were classified as abnormal.

Spatial neglect. Spatial neglect was assessed using the Apple Cancellation task (Bickerton et al., 2011; Chechlacz et al., 2010 [Chapter 2]), which is part of the Birmingham University Cognitive Screen (BUCS; www.bucs.bham.ac.uk). The Apple Cancellation task is similar to the gap detection task by Ota et al. (2001) and is designed to simultaneously measure spatial and object-based neglect. Participants were presented with a page (A4) in landscape orientation with 50 apples divided into 5 invisible columns, one middle, one near

left, one far left, one near right and one far right. Each column contains 10 complete apples (targets) along with distractors, which are apples with either a left or a right part missing (incomplete apples). Spatial neglect is measured by whether patients miss targets (complete apples) on one side of the page. Object-based neglect is measured by whether patients make false positive responses by cancelling distractors i.e. incomplete apples. In the neuroimaging analyses we used normalized asymmetry scores for left and right spatial neglect from the Apple Cancellation task (see Chechlacz et al., 2010 [Chapter 2], for details). The cut off scores for spatial neglect based on Apple Cancelation task are as follows: asymmetry for full apples <-2 right side errors or >3 left side errors; total numbers of target omissions i.e. accuracy score 40/50.

Tactile extinction. The task consisted of 4 unilateral left, 4 unilateral right and 8 bilateral trials. Testing for tactile extinction was achieved by applying a light touch to the right hand (right unilateral trial), left hand (left unilateral trial) or both hands simultaneously (bilateral trial). For the neuroimaging analyses of tactile extinction we calculated left and right asymmetry scores on two item trials and on unilateral trials as well as an extinction index (scored as for visual extinction, see above). These data were entered into the statistical models.

Each patient's behavioural performance was classified based on cut offs drawn from the BUCS. Patients were classed as having a clinical deficit on measures of tactile extinction if their scores on the task fell outside the control norms taken from 70 healthy controls without history of brain lesion or any neurological disorders. The cut off scores for tactile extinction task are as follows: unilateral trials (both left and right) <4 impaired; left bilateral trials <7 impaired; right bilateral participants younger than 74 years old < 8 impaired and participants older than 75 years old <7 impaired.

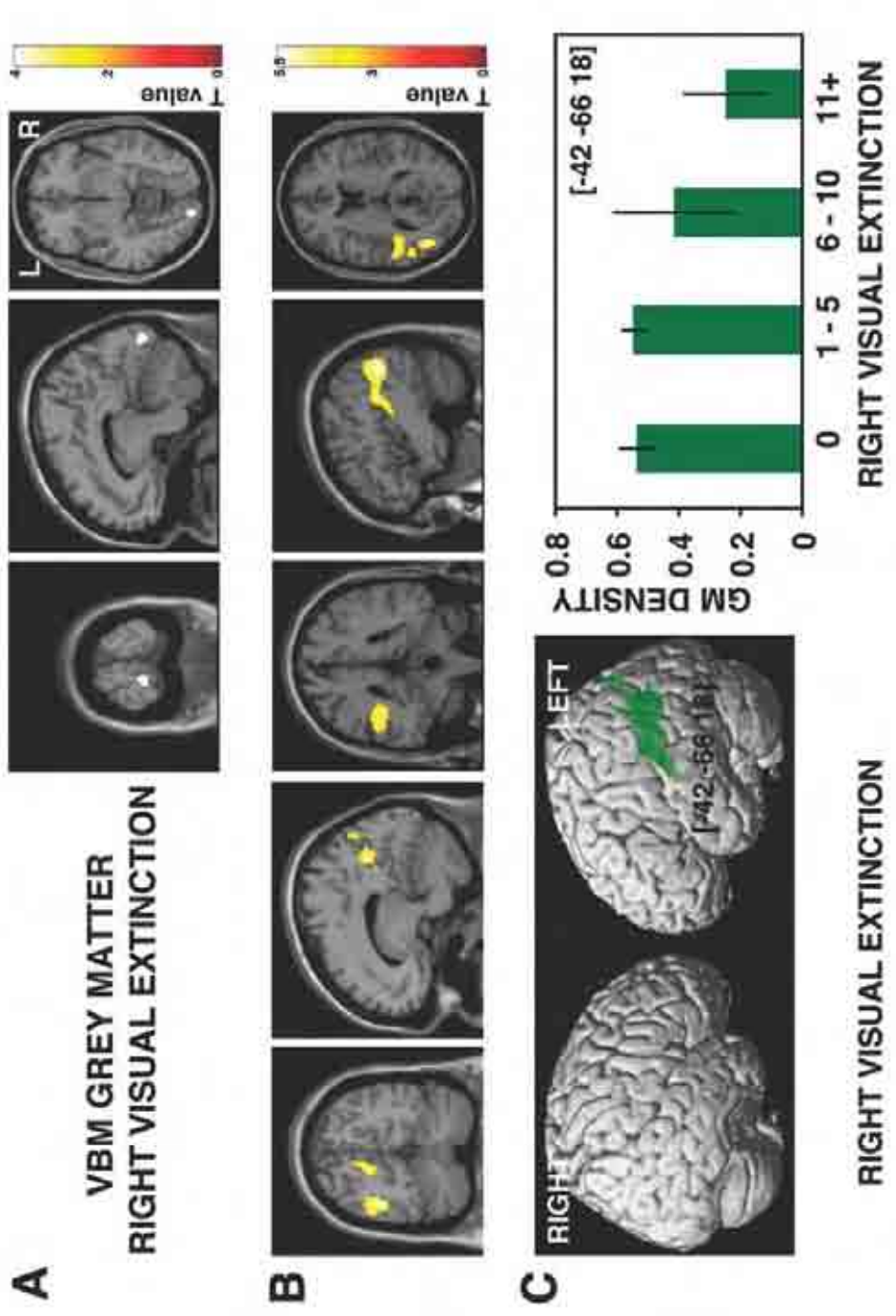

Figure 7. Neuronal substrates of right visual extinction: VBM analysis of grey matter. Results from Analysis 1 depicting **(A)** grey matter substrates contributing to right visual field deficits/visual neglect problems (performance on 1-item/unilateral trials; right unilateral asymmetry score) and **(B)** right visual extinction (right visual extinction index). Please note that in **A** and **B** the lesioned areas are coloured according to the significance level in the VBM analysis, where brighter colour means higher t-value. **(C)** To further illustrate the relationship between grey matter loss and right visual extinction deficits, we first extracted the principal eigenvariate of the voxels within the entire main cluster identified in VBM analysis (cluster with MNI coordinates -42-66 18 shown on brain render) and plotted against the visual extinction score (right visual extinction index).

We report the performance of individual patients on the visual extinction, tactile extinction and Apple cancellation tasks in Table 4, together with the clinical and demographic details for the patients. Note that although we used cut off scores to estimate the number of patients with visual extinction, spatial neglect and tactile extinction (see Table 4), in all neuroimaging analyses (see below) the behavioural measurements were treated as continuous variables and not as categorical scores.

Neuroimaging assessment

Patients and healthy controls were scanned at BUIC on a 3T Philips Achieva MRI system with 8-channel phased array SENSE head coil. The scans were obtained in close proximity to the time of behavioural testing. The anatomical scan was acquired using a sagittal T1-weighted sequence (sagittal orientation, TE/TR=3.8/8.4ms, voxel size 1x1x1mm^3).

Image pre-processing

T1 scans from patients and healthy controls were first converted and reoriented using MRICro (Chris Rorden, Georgia Tech, Atlanta, GA, USA). Pre-processing was done in SPM5 (Statistical Parametric Mapping, Welcome Department of Cognitive Neurology, London UK). The brain scans were transformed into the standard MNI space using the unified-segmentation procedure (Ashburner and Friston, 2005). The unified-segmentation procedure involves tissue classification based on the signal intensity in each voxel and on a-priori knowledge of the expected localization of grey matter (GM), white matter (WM), cerebrospinal fluid (CSF) in the brain. To further improve tissue classification and spatial normalization of lesioned brains we used a modified segmentation procedure (Seghier et al., 2008). This protocol was developed to resolve problems with misclassification of damaged tissue by including an

additional prior for an atypical tissue class (an added "extra" class) to account for the "abnormal" voxels within lesions and thus allowing classification of the outlier voxels (Seghier et al., 2008). While earlier versions of SPM struggled with normalizing and segmenting brains containing large lesions (e.g. Stamatakis and Tyler, 2005) the unified-segment procedure as implemented in SPM5 has been shown to be optimal for spatial normalization of lesioned brains (Crinion et al., 2007). Following segmentation, we visually inspected each of the segmented scans to assess whether segmentation and normalisation was successful. Finally, the segmented images were smoothed with 8 mm FWHM Gaussian filter to accommodate the assumption of random field theory used in the statistical analysis (Worsley, 2003). The choice of intermediate smoothing of 8mm FWHM was previously shown to be optimal for lesion detection and further analysis of segmented images (e.g. Leff et al., 2009; Seghier et al., 2008; Stamatakis and Tyler, 2005).

The pre-processed GM and WM images were used for automated lesion identification using fuzzy clustering (Seghier et al., 2008) and in the voxel-based analyses to determine the relationships between lesion site and visuospatial deficits. Previous work (e.g. Leff et al., 2009; Price et al., 2010) has demonstrated that the modified segmentation protocol combined with VBM is successful in facilitating the understanding of brain behaviour relationships in neurological patients.

Automated lesion identification

Lesion maps from individual patients were reconstructed using a modified segmentation procedure (see above) and an outlier detection algorithm based on fuzzy clustering (for a description of the full procedure including validation based on real and simulated lesions on T1-weighted scans, see Seghier et al., 2008). This procedure identifies

voxels that are different in the lesioned brain as compared to a set of healthy controls (here we employed a set of 100 healthy controls as described above) using normalised grey and white matter segments. The GM and WM outlier voxels are then combined into a single outlier image and thresholded to generate a binary map of the lesion (Seghier et al., 2008). The results of lesion reconstruction were verified against the patient's T1 scans. We next overlaid the lesions for all 50 patients. The lesion overlay map was created to represent the spatial distribution of lesions in our group of patients (see Supplementary Figure 2, Appendix 2). The GM and WM lesion volumes for each patient were calculated using Matlab 7.5 (The MathWorks, Natick, MA, USA) based on individual lesions from automated lesion identification procedure (see above) and subsequent GM and WM masks were defined using the WFU Pick atlas software toolbox in conjunction with SPM5 (Maldjian et al., 2003). The estimated GM and WM lesion volumes of all individual patients were used as covariates in the statistical analyses (see below).

Voxel-based morphometry (VBM)

To assess the relationship between WM and GM damage and visual extinction scores on a voxel-by voxel basis, we used VBM approach (Ashburner and Friston, 2000) and carried out statistical analyses with SPM5 using smoothed GM and WM maps obtained from segmented scans from our patient sample (see above for the pre-processing protocol). We used parametric statistics within the framework of the general linear model (Kiebel and Holmes, 2003) and the analyses for WM and GM were carried out separately. In each statistical model age, handedness, gender, type of lesion and time since diagnosis were included as covariates of no interest. We also entered as covariates the estimated volume of either grey or white matter tissue loss (lesion volume) respectively for each type of analysis

(statistical analysis with GM or WM maps). All these covariates ensured that we could control for various confounding factors that potentially might have affected cognitive performance.

We used three statistical models for both GM and WM analyses. *Analysis 1* was carried out to examine the relationship between the lesion(s) and left and right visual extinction. In the statistical model for *Analysis 1* we included four behavioural measures of visuospatial problems: left and right asymmetry scores on unilateral trials and left and right visual extinction indices (extracted from the computer task, see above). This enabled us to examine the neuronal substrates of left and right visual extinction with effects of unilateral biases eliminated. Given that the unilateral biases were measured by effects of poor report of a single item presented for a reasonably brief period (200 ms) in the contralesional field, then poor performance could reflect either a visual field defect or visual neglect, both of which may co-vary with extinction. Dissociating visual extinction from hemifield/visual neglect problems was achieved by using exclusive masking, i.e. testing for a change in voxel intensity that correlated with left or right "visual extinction" (the left or right visual extinction index) but not with left or right deficits on a single item trials. *Analysis 2* was carried out to further examine the relationship between the neuronal substrates of visual extinction and spatial neglect. This analysis included the same covariates as *Analysis 1* plus two additional measures: left and right spatial neglect, extracted from the Apple Cancellation task (see above). Bickerton et al. (2011) report data indicating that measures of neglect derived from the Apple Cancellation task dissociate from visual field defects (measured using confrontation testing). *Analysis 2* aimed to formally test for common and dissociated neuronal substrates that contribute to visual extinction and spatial neglect. Patients in our study predominantly suffered from left deficits (Table 4) and therefore we restricted *Analysis 2* to left visual

extinction and left spatial neglect. Dissociating left visual extinction from left spatial neglect was achieved by using exclusive masking, i.e. testing for a change in voxel intensity that correlated with left visual extinction ($p < 0.001$, uncorrected) but not with left spatial neglect ($p > 0.05$, uncorrected) and vice versa, and the common mechanisms were tested by using an inclusive mask - i.e. selecting all voxels common to both left visual extinction and left spatial neglect. To further verify the visual extinction versus neglect dissociations, we report in the tables the results (F-tests) of the interaction between visual extinction and spatial neglect regressors. *Analysis 3* examined the relationship between the neuronal substrates of visual and tactile extinction. This analysis included the same covariates as *Analysis 1* plus four additional measures: left and right tactile asymmetry scores on unilateral trials and left and right tactile extinction indices, extracted from the BUCS tactile extinction task (see above). This enabled us to control and formally test common and dissociated neuronal substrates that contribute to visual and tactile extinction. Similarly to *Analysis 2*, we restricted *Analysis 3* to left deficits. Dissociating left visual from left tactile extinction was achieved by using exclusive masking, i.e. testing for a change in voxel intensity that correlated with visual extinction (left visual extinction index score; $p < 0.001$, uncorrected) but not with left tactile extinction (left tactile extinction index score; $p > 0.05$, uncorrected) and vice versa. Common mechanisms were tested by using an inclusive mask - i.e. selecting all voxels common to both left visual and left tactile extinction. To further verify the visual versus tactile extinction dissociations, we report in the tables the results (F-tests) of the interaction between the visual and tactile regressors.

We report only results that showed significant effect at $p< 0.001$ cluster-level corrected for multiple comparison with amplitude of voxels surviving of $p< 0.001$ uncorrected across the whole brain and an extent threshold of $200mm^3$ (>100 voxels). The brain coordinates are presented in standardized MNI space. The anatomical localization of the

lesion sites within the grey matter was based on the Anatomical Automatic Labeling toolbox (AAL toolbox, Tzourio-Mazoyer et al., 2002), the Duvernoy Human Brain Atlas (Duvernoy et al., 1991) and the Woolsey Brain Atlas (Woolsey et al., 2008). In order to localize white matter lesions associated with visual extinction in relation to specific white matter pathways we used the JHU White matter tractography atlas (Hua et al., 2008) and the MRI Atlas of Human White Matter by (Mori, 2005). To further evaluate damage within specific white matter tracts associated with spatial attention deficits we employed the SPM Anatomy toolbox with cytoarchitectonic probabilistic maps of human white matter fibre tracts (Burgel et al., 2006; Eickhoff et al., 2005). Specifically, we used the overlap function from the Anatomy toolbox to estimate the number of overlapping voxels between the WM statistical maps based on VBM analyses and probabilistic fibre tract maps for the superior longitudinal fasciculus (SLF; Burgel et al., 2006). We have limited the analyses based on the Anatomy toolbox to the SLF because other pathways of interests are either not represented in this toolbox (in particular inferior longitudinal fasciculus, ILF) or have a known poor correspondence between cytoarchitectonic probabilistic post-mortem histology and in vivo tractography based atlases (in particular inferior fronto-occipital fasciculus, IFOF; Thiebaut de Schotten et al., 2011).

RESULTS

Table 4 shows the performance of individual patients on the visual extinction, Apple Cancelation task and tactile extinction tests together with patients' clinical and demographic details. 24 patients showed left- and 14 right-bilateral bias on two-item trials in the visual extinction task. Out of these, 17 patients were classified as having left visual extinction and 11 as having right visual extinction with varied severity of impairments (based on the

extinction index scores). 9 patients showed left and 4 right spatial neglect based on the Apple Cancellation task. Finally 12 patients showed left and 2 right-side bias on two-item trials in the tactile extinction task. Out of these, 11 patients were classified as having left tactile extinction and 2 as having right tactile extinction, with the severity of the impairments reflected in the extinction index scores. The number of patients with visual extinction, spatial neglect and tactile extinction as listed above was estimated based on cut off scores. However, in all neuroimaging analyses (see below) we did not use these binary classifications; all the behavioural measurements of spatial attention deficits were treated as continuous variables and not as categorical scores.

The present study pooled neuropsychological patients with different aetiologies, such as stroke, carbon monoxide poisoning and degenerative changes. The working assumption that guided our neuroimaging analyses was that while different aetiologies can lead to different distributions of lesions, it still remains the case that a cognitive deficit can result from specific anatomical lesions. Therefore, such an approach facilitates the understanding of brain behaviour relationship by generalizing the inferences across neurological conditions i.e. by pooling across different aetiologies we investigated the neuroanatomy of the spatial attention deficits rather then spatial attention deficits following a specific pathology (i.e. stroke)[11].

[11] All patients included in this study were chronic and out of 50 patients, only three suffered from carbon monoxide poisoning and five from degenerative changes (three of these patients also suffered from different forms of unspecified vascular disease causing additional acquired focal brain lesions). Omitting the small number of non-stroke patients from the analyses made little difference to the results. These patients are included in all analyses reported here to maximise power.

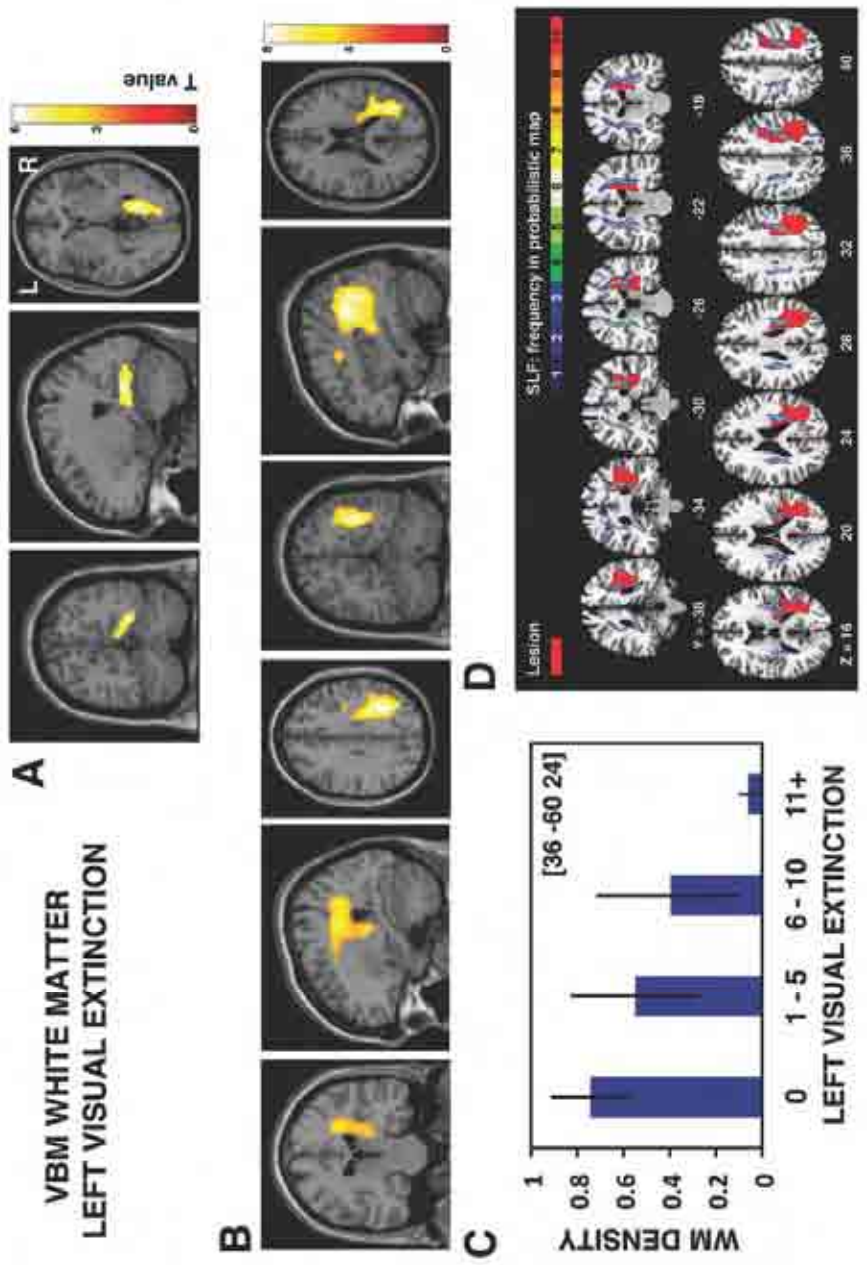

Figure 8. Neuronal substrates of left visual extinction: VBM analysis of white matter. Results from Analysis 1 depicting **(A)** white matter substrates contributing to left visual field deficits/visual neglect problems (performance on 1-item/unilateral trials; left unilateral asymmetry score) and **(B)** left visual extinction (left visual extinction index). Please note that in **A** and **B** the lesioned areas are coloured according to the significance level in the VBM analysis, where brighter colour means higher t-value. **(C)** To further illustrate the relationship between white matter loss and left visual extinction deficits, we first extracted the principal eigenvariate of the voxels within the entire main cluster identified in VBM analysis (cluster with MNI coordinates 36 -60 24) and plotted against the visual extinction score (left visual extinction index). **(D)** Link between SLF damages and left visual extinction deficits illustrated by overlap between the statistical lesion maps obtained from the VBM analyses of white matter (lesion in red) and the cytoarchitectonic probabilistic maps of the SLF from the JŸlich atlas. MNI coordinates of coronal and axial sections are given.

Grey and white matter substrates of visual extinction deficits: Analysis 1

Analysis 1 examined the relationship between the behavioural measures of left and right visual extinction and structural damage within grey and white matter. In this analysis we used separate covariates representing unilateral bias (asymmetry score on unilateral trials) and visual extinction (the extinction indices) to dissociate (through exclusive masking) the neuronal structures contributing to visual field deficits/neglect (performance on 1-item/unilateral trials) versus the 2-item spatial bias (the difference in the asymmetry score on 1 vs. 2-item trials) across the left and right sides of visual space. Grey matter damage within the left and right calcarine sulci (Figure 6A and Figure 7A; Table 5) and white matter damage corresponding to the location of IFOF and the optic radiation was associated with a measure of contralateral visual field deficits/neglect (i.e. when unilateral stimuli were missed; see Figures 8A and 9A; Table 6). This analysis provides a validation of the present VBM method since it reveals a clear link between damage to visual cortex and a measure of a visual field defect (poor unilateral performance). Left visual extinction was associated with grey matter lesions in the right hemisphere within the inferior parietal lobule (angular and supramarginal gyri), the insula, TPJ, superior temporal sulcus, medial temporal gyrus, medial occipital gyrus, medial frontal gyrus and putamen (Figure 6B; Table 5). We also found an association with white matter lesions consistent with damage within the SLF, IFOF, ILF and internal capsule (including the thalamic radiations; Figure 8B; Table 6). Right visual extinction was associated with unilateral grey matter damage in the left hemisphere within the inferior parietal lobule (angular and supramarginal gyri), precuneus, superior temporal sulcus, TPJ, medial temporal gyrus and medial occipital gyrus (Figure 7B; Table 5). Right extinction was also linked to white matter lesions consistent with damage to the SLF, IFOF, ILF and the internal capsule (including the thalamic radiations; Figure 9B; Table 6).

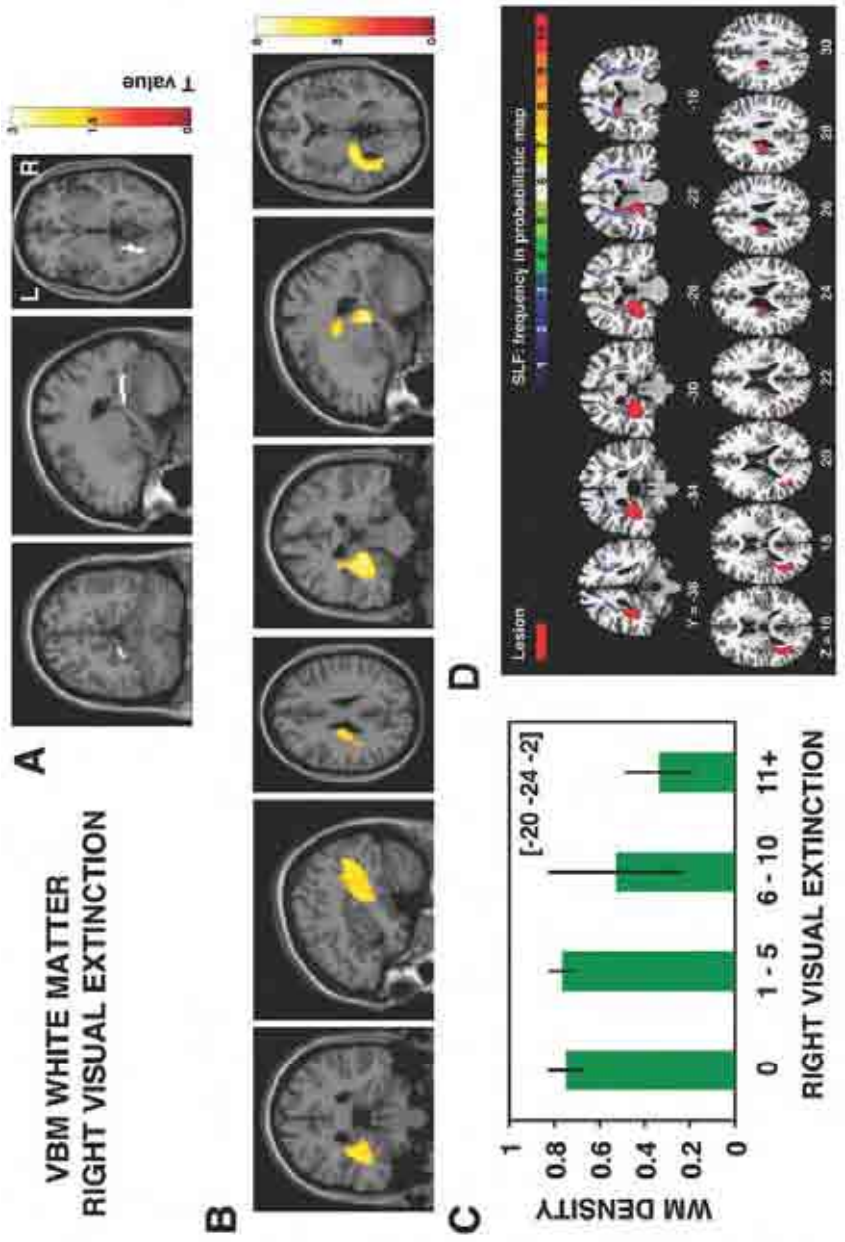

Figure 9. Neuronal substrates of right visual extinction: VBM analysis of white matter. Results from Analysis 1 depicting **(A)** white matter substrates contributing to right visual field deficits/visual neglect problems (performance on 1-item/unilateral trials; right unilateral asymmetry score) and **(B)** right visual extinction (right visual extinction index). Please note that in **A** and **B** the lesioned areas are coloured according to the significance level in the VBM analysis, where brighter colour means higher t-value. **(C)** To further illustrate the relationship between white matter loss and right visual extinction deficits, we first extracted the principal eigenvariate of the voxels within the entire main cluster identified in VBM analysis (cluster with MNI coordinates -20 -24 -2) and plotted against the visual extinction score (right visual extinction index). **(D)** Link between SLF damages and right visual extinction deficits illustrated by overlap between the statistical lesion maps obtained from the VBM analyses of white matter (lesion in red) and the cytoarchitectonic probabilistic maps of the SLF from the JŸich atlas. MNI coordinates of coronal and axial sections are given.

To further illustrate the relationship between grey and white matter loss and visual extinction deficits, we first extracted the principal eigenvariate of the voxels within the entire main cluster identified in VBM analysis and plotted this against the visual extinction index score (Figure 6C, 7C, 8C and 9C). As SLF is considered one of the main components of the fronto-parietal attention network (Bartolomeo et al., 2007; Makris et al., 2005; Mesulam, 1981; Petrides and Pandya, 2006; Schmahmann and Pandya, 2006; Thiebaut de Schotten et al., 2005), we next carried out further analysis to examine the link between SLF damage and visual extinction deficits using the cytoarchitectonic probabilistic maps from the Jülich probabilistic atlas (Burgel et al., 2006). Overlap of the statistical lesion maps obtained from the VBM analyses and the probabilistic maps of the left and right SLF confirmed that damage within the right SLF was associated with left visual extinction deficits and damage within the left SLF was associated with right visual extinction deficits. 91% of the voxels attributed to the right SLF within the probability map from the Jülich atlas coincided with the cluster representing the white matter lesion associated with left visual extinction (i.e. the intersection volume between the representation of the right SLF and the VBM cluster was 91% of the all attributed voxels; Figure 8D). We also found that 24% of voxels attributed to the left SLF within the probability map from the Jülich atlas coincided with the cluster representing white matter lesion associated with right visual extinction (Figure 9D).

Grey and white matter substrates of visual extinction versus spatial neglect: Analysis 2 (Left deficits only)

As patients with visual extinction often experience other visuospatial problems including spatial neglect, we next attempted to separate the neural correlates of the different visuospatial processing disorders. Using exclusive masking we found that grey matter lesions

in the right hemisphere within the angular gyrus and superior temporal sulcus were associated specifically with left visual extinction, with these lesions also extending into the insula and middle occipital gyrus. In contrast right hemisphere damage within the supramarginal gyrus, the intraparietal sulcus, the middle frontal gyrus and superior temporal gyrus (extending partially into middle temporal gyrus) were exclusively associated with left spatial neglect (Figure 10A, top panel; Table 7). The VBM analyses of white matter showed that left visual extinction was linked with lesions in the right hemisphere consistent with damage to the SLF, IFOF, ILF and thalamic radiations. Left spatial neglect was also associated with lesions suggesting damage within IFOF and the internal capsule (including the thalamic radiations; Figure 10B; Table 8). Inclusive masking showed that both left visual extinction and left spatial neglect were associated with damage to the right hemisphere in the middle frontal area (BA46), the TPJ, the middle temporal gyrus, a small region within inferior parietal lobule (borderline between angular and supramarginal gyri), the insula and putamen (Figure 10A, bottom panel; Table 7). The white matter analysis highlighted that both left visual extinction and left spatial neglect were associated with right hemisphere lesions of the SLF and the thalamic radiations (Figure 10B; Table 8).

We next carried out further analyses to examine the link between SLF damage and both visuospatial visual extinction and spatial neglect using cytoarchitectonic probabilistic maps from the Jülich probabilistic atlas (Burgel et al., 2006). Overlap of the statistical lesion maps obtained from the VBM analyses with inclusive masking and the probabilistic maps of the right SLF confirmed that damage within the right SLF was associated with the common effect of lesion. 32% of the voxels attributed to the right SLF within the probability map coincided with the cluster representing the white matter lesion associated with both left visual extinction and spatial neglect (Figure 10C).

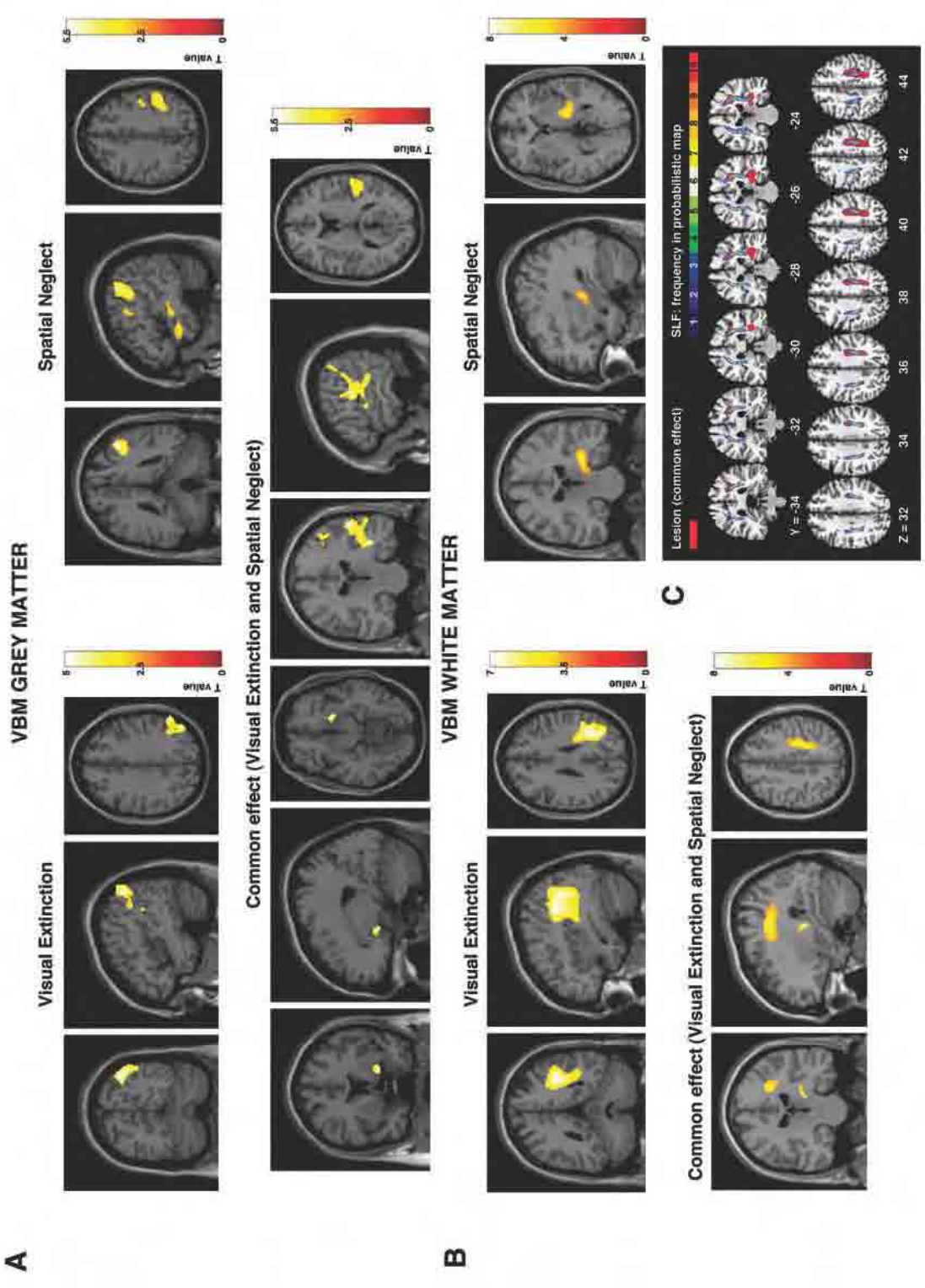

Figure 10. Neuronal substrates of visual extinction versus spatial neglect: VBM analysis of grey and white matter. (A) VBM results showing voxels corresponding to grey matter damage in left visual extinction only (exclusive masking), left spatial neglect only (exclusive masking) and both forms of deficits (inclusive masking). **(B)** VBM results showing voxels corresponding to white matter damage in left visual extinction only (exclusive masking), left spatial neglect only (exclusive masking) and both forms of deficits (common effect; inclusive

masking). Please note that in **A** and **B** the lesioned areas are coloured according to the significance level in the VBM analysis, where brighter colour means higher t-value. (**C)** Link between SLF damages and common effect of lesions associated with both types of deficits illustrated by overlap between the statistical lesion maps obtained from the VBM analyses of white matter (lesion in red) and the cytoarchitectonic probabilistic maps of the SLF from the Jülich atlas. MNI coordinates of coronal and axial sections are given.

Grey and white matter substrates of visual versus tactile extinction: Analysis 3 (Left side deficits only)

By using exclusive masking we found that grey matter lesions in the right hemisphere within the angular gyrus, the superior temporal sulcus extending into the middle temporal gyrus and the middle occipital gyrus were associated with left visual extinction. In contrast right hemisphere damage within the postcentral gyrus and putamen were associated with left tactile extinction (Figure 11A, top panel; Table 9). The occurrence of both visual and tactile extinction (inclusive masking) was associated with damage to the right TPJ (Figure 11A, bottom panel; Table 9).

The VBM analyses of white matter using exclusive masking showed that lesions in the right hemisphere consistent with damage to the SLF, IFOF and thalamic radiations were associated with left visual extinction. Left tactile extinction was exclusively associated with lesions consistent to damage within the internal capsule and the ILF (Figure 11B; Table 10). The presence of both left visual and tactile extinction (inclusive masking) was consistent with damage to the right SLF (Figure 11B; Table 10). We carried out further analysis to examine the link between SLF damage and both types of extinction using cytoarchitectonic probabilistic maps from the Jülich probabilistic atlas (Burgel et al., 2006). Overlap of the statistical lesion maps obtained from the VBM analyses with inclusive masking and the probabilistic maps of the right SLF confirmed that damage within the right SLF was associated the common effect of lesion. 18.6% of the voxels attributed to the right SLF within

probability map from the Jülich atlas coincided with the cluster representing the white matter lesion associated with both left visual and tactile extinction (Figure 11C).

DISCUSSION

The current study examined functional and modality-specific specialization within the parietal cortex and associated attention networks in relation to clinical deficits in extinction and spatial (egocentric) neglect. Prior lesion-symptom-mapping studies provide clear evidence supporting functional specialization within parietal cortex and associated spatial attention networks (e.g., Hillis et al., 2005; Karnath et al., 2003; Mort et al., 2003; Vallar et al., 1994; Vandenberghe and Gillebert, 2009). One of the limitations of previous reports is that often they looked at the link between single components of visuospatial attention and/or they used all-or-none classifications of deficits in patients (insensitive to the magnitude of the deficit). In addition, effects of potentially co-varying factors, such as age, time since lesion and lesion volume, have not been taken into account. Perhaps not surprisingly, there are discrepancies between different patient studies and also discrepancy between lesion-symptom-mapping studies and fMRI and TMS studies in healthy controls (e.g., Battelli et al., 2009; Cicek et al., 2007; Karnath et al., 2003; Meister et al., 2006; Pascual-Leone et al., 1994; Ticini et al., 2010; Vandenberghe et al., 2000; Vandenberghe et al., 2005; Vandenberghe and Gillebert, 2009). The present study advanced this prior work in various ways. We (i) used sample of patients not specifically selected for the deficits, (ii) examined continuous variations in performance instead of categorical assignment of patients into groups with and without the specific deficit(s), (iii) extracted out co-varying factors in our modelling of the data and (iv) examined the relations between the lesions linked to visual extinction and those related to visual field defects /neglect (Analysis 1) and spatial neglect (Analysis 2). In

addition, we examined the neural substrates of modality-specific extinction (visual versus tactile; Analysis 3). Finally, to provide comprehensive neuroanatomical analyses we performed a whole brain evaluation of both grey and white matter integrity. We report here several important results concerning (1) the cortical and basal ganglia correlates of visual extinction in relation to visual field defects, unilateral neglect, and tactile extinction, and (2) the sub-cortical white matter correlates of extinction and neglect. We consider these issues in turn. We also discuss potential implications of our data for right hemisphere bias in the control of visuospatial attention.

Cortical and basal ganglia correlates of extinction, visual field defects and neglect

Our lesion-symptom analysis provides a clear distinction between the grey matter lesions related to poor unilateral performance with briefly presented stimuli and the lesions associated with visual extinction. Poor unilateral performance was linked to damage to inputs coming into and structures within primary visual cortex. Visual extinction was linked to damage to the inferior parietal lobe (angular and supramarginal gyri), the STS, the medial frontal, temporal and occipital gyri and the TPJ. These data indicate that visual extinction can be dissociated from deficits caused primarily by a sensory loss (Analysis 1).

The neural structures associated with visual extinction had both common and distinct regions with those associated with unilateral neglect (Analysis 2). Damage to the angular gyrus, the superior temporal sulcus and the middle occipital gyrus and the insula were linked to extinction. Lesions involving the supramarginal gyrus, the IPS, the middle frontal and the superior temporal gyri were associated exclusively with spatial (egocentric) neglect. Lesions affecting the TPJ, the middle temporal region, the middle frontal area BA46 and the insula and putamen were linked to the presence of both neglect (measured on a cancellation task)

and extinction. This pattern of common and also distinct lesions associated with extinction and with neglect can help explain why patients can present with both disorders (e.g., Karnath et al., 2003; Manes et al., 1999; Rees et al., 2000; Vuilleumier and Rafal, 2000) but also why dissociations can occur across different patients (e.g., Cocchini et al., 1999; Karnath et al., 2003; Ogden, 1985; Ticini et al., 2010; Vallar et al., 1994). The scanning task used to measure neglect likely involves several processes additional to those required by the extinction task, including the ability to orient attention across wider areas of space, to make eye movements and to remember previously scanned locations. It is possible that the neural regions exclusively linked to neglect comprise these additional processes (see also Karnath et al., 2003; Pavlovskaya et al., 2007). On the other hand, our extinction task required patients to assimilate briefly presented stimuli maintaining a balance in the resources given to the left and right locations, and it penalised patients who showed prolonged disengagement of attention from the first to the second item selected for report. The brain regions exclusive to extinction may reflect these processes. Interestingly Chechlacz et al. (2010) reported that what they termed ‘allocentric neglect’ was associated with damage to the regions similar to these associated with extinction here. Their measure of allocentric neglect demanded that patients discriminate the left and right sides of individual objects irrespective of the position of the objects in the visual field. A failure to balance resources when the left and right sides of an object or region of space are being assimilated together could lead to both extinction and allocentric neglect. Although consistent with the notion that extinction and allocentric neglect might be subserved by the same cortical sites and processing mechanisms, it should be noted here that several studies based on lesion data including reports using diffusion-perfusion MRI provide converging evidence that the middle temporal gyrus codes the left and right sides of individual objects irrespective of their position in the visual field (Committeri, et al., 2004;

Khurshid et al., 2011; Medina et al., 2009; Verdon et al., 2010). Whether the extinction measure reflects the relative rather than absolute positions of the stimuli remains to be explored.

In contrast to these exclusive regions, we also found that damage to the TPJ, the middle temporal gyrus, the insula and putamen generated both visual extinction and neglect. These regions appear to play a common role in the extinction task with brief stimulus presentations and the ability to scan and cancel targets across space (measured in the Apple cancellation task). One potential candidate here is a mechanism that detects the presence of a stimulus made available for selection by earlier perceptual processes and that passes on the selected stimulus to regions involved in forming an explicit response. This process of selecting response-relevant stimuli has recently been modelled by Mavritsaki et al. (2010). In this model visual stimuli compete for selection with the 'winner' emerging based either on bottom-up differences relative to other stimuli or on a match to top-down expectancies. The winner activates a saliency map where activity reflects the emergence of 'winner takes all' activity over time. Mavritsaki et al. (2010) simulated search in their model and then correlated the time series for the haemodynamic function predicted by the model with that found in fMRI experiments examining visual search. They found that activity summed across the saliency map exclusively correlated with BOLD activity in the right TPJ, consistent with this brain region providing a signal about the emergence of a target over time. Damage to the computation of this signal for elements on one side of space or one side of an object would lead to impaired perceptual report, both under the conditions we used to measure neglect (Apple cancellation) and extinction.

Our argument concerning the functional role of the TPJ in selection bears similarities to proposals made by Corbetta and Shulman (2002) that the right TPJ in particular acts as a

'circuit breaker' responding to bottom-up salient stimuli. Our account extends this argument, however, to suggest that the TPJ's role in selection is sensitive to top-down as well as bottom-up cues (see also Riddoch et al., 2010), for a more detailed argument). This more extended account fits with other neuroimaging data showing TPJ activation in relation to target-related features (Downar et al., 2001). Also, our data indicate that the left and right TPJs are involved respectively with right and left-side extinction. This in turn suggests that this salience-detection function of the TPJ is bilateral, though the right TPJ may play a more dominant role (cf. Corbetta and Shulman, 2002; Mavritsaki et al., 2010); see also below for further discussion about right hemisphere dominance in visuospatial attention network).

It is also noteworthy that our analysis of the relations between visual and tactile extinction highlighted the TPJ as being the common site of deficit for both modalities. This result indicates that the right TPJ may serve to detect the presence of a target in a multi-modal spatial representation, so that damage to this region disrupts responses to the left item from the two tactile as well as two visual targets. These findings are consistent with prior neuroimaging findings in healthy participants showing the involvement of the TPJ across multiple sensory modalities: visual, tactile and auditory (Corbetta and Shulman, 2002; Downar et al., 2000, 2002). Although Ticini et al. (2010) did not test the neuronal substrates of multimodal extinction, they noted that numerous patients with visual extinction resulting from cortical malperfusion within the TPJ had either concurrent tactile or concurrent auditory extinction. Taken together, our findings contribute to growing body of evidence that the TPJ plays a general role in identifying salient events in the sensory environment across multiple modalities. It follows that the TPJ is an important component of the multimodal network consisting of temporo-parietal and frontal substrates mediating attention and awareness of salient stimuli (Downar et al., 2002; Mesulam, 1981).

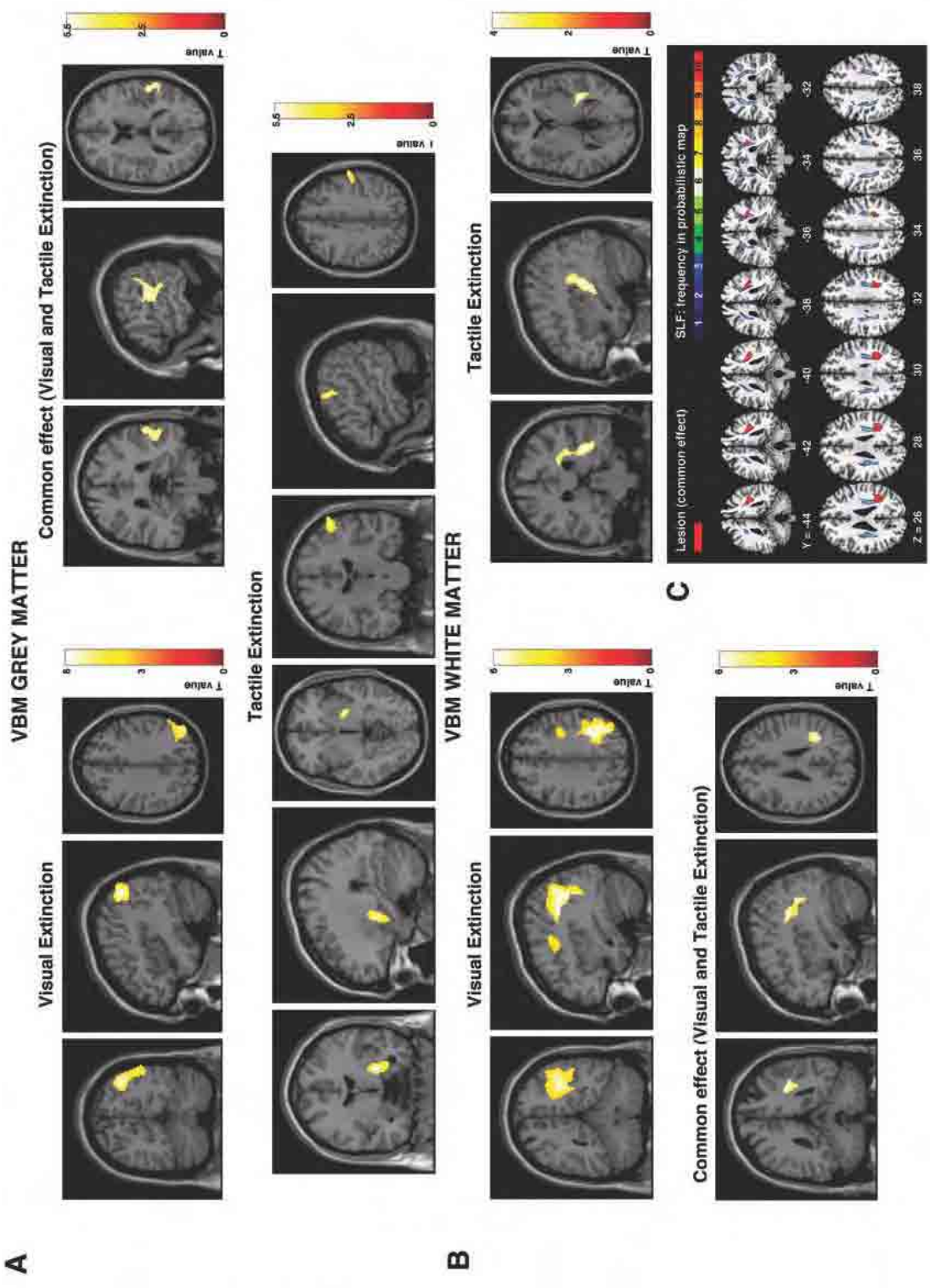

Figure 11. Neuronal substrates of visual versus tactile extinction: VBM analysis of grey and white matter. (A) VBM results showing voxels corresponding to grey matter damage in left visual extinction only (exclusive masking), left tactile extinction only (exclusive masking) and both forms of deficits (inclusive masking). **(B)** VBM results showing voxels corresponding to white matter damage in left visual extinction only (exclusive masking), left tactile extinction only (exclusive masking) and both forms of deficits (common effect;

inclusive masking). Please note that in **A** and **B** the lesioned areas are coloured according to the significance level in the VBM analysis, where brighter colour means higher t-value. (**C)** Link between SLF damages and common effect of lesions associated with both types of deficits illustrated by overlap between the statistical lesion maps obtained from the VBM analyses of white matter (lesion in red) and the cytoarchitectonic probabilistic maps of the SLF from the Jülich atlas. MNI coordinates of coronal and axial sections are given.

The present study also found that damage to the putamen was linked to both visual extinction and neglect. As noted in the Introduction, prior studies have found that damage to the basal ganglia, even without concomitant cortical lesions, is associated with spatial (egocentric) neglect (Karnath et al., 2002). The same research group also linked lesions within basal ganglia to poor perfusion in the region around the TPJ resulting in visual extinction (Ticini et al., 2010). On one hand the data point to a role of sub-cortical structures such as the basal ganglia playing an interactive role with cortical regions involved in visuospatial selection, which is not surprising taking into account direct anatomical connection to different cortical regions (Yeterian and Pandya, 1993, 1995, 1998). There is also evidence that lesions including axonal damage within one brain region may cause functional and metabolic abnormalities via distant regions (Carmichael et al., 2004; Feeney and Baron, 1986). Thus damage to the critical sub-cortical structures may subsequently lead to reduced perfusion and functional disruptions in processing at a cortical level and it seems plausible that damage to subcortical structures alone may not be sufficient to result in visuospatial deficits (see Ticini et al., 2010) for further discussion).

Sub-cortical white matter correlates of extinction and neglect

Our white matter analyses point to the critical role of the SLF as a pathway interconnecting components of the visuospatial attention network. Damage to this pathway disrupts interactivity within the network, and biases selection against the affected hemisphere.

These results are consistent with previous work highlighting the SLF as the main components of the fronto-parietal attention network (Bartolomeo et al., 2007; Makris et al., 2005; Mesulam, 1981; Petrides and Pandya, 2006; Schmahmann and Pandya, 2006; Thiebaut de Schotten et al., 2005). Our white matter findings fit well with both anatomical accounts of SLF (Makris et al., 2005; Schmahmann and Pandya, 2006; Schmahmann et al., 2007) and with grey matter correlates of extinction and neglect. The SLF connects temporo-parietal association areas with the frontal lobes and is composed of three main fibre bundles: SLF I, SLF II and SLF III (Makris et al., 2005; Petrides and Pandya, 1984, 1988, 2002; Schmahmann and Pandya, 2006; Schmahmann et al., 2007). SLF I links the superior parietal and adjacent medial parietal cortex with the superior frontal lobes and extends to the dorsal premotor and dorsolateral prefrontal regions. SLF II connects the caudal inferior parietal lobule (angulat gyrus) and intraparietal sulcus with caudal-lateral prefrontal cortex. SLF III links rostral inferior parietal lobule (supramarginal gyrus) to the ventral part of the premotor and prefrontal cortex. The fourth subdivision of the SLF, the arcuate fasciculus (AF), originates from the caudal part of the superior temporal gyrus arches around the caudal end of the lateral sulcus and extends to the lateral prefrontal cortex along with the fibers of SLF II. Some anatomical studies indicate that the SLF and AF have discrete trajectories and should be considered as a separate pathways (for review see Makris et al., 2005; Schmahmann et al., 2007). The scope of the current paper does not permit drawing any conclusions about functional specialization of different subcomponents of the SLF i.e. linking specific cognitive deficits with damage to separate subcomponents of SLF.

The numerous earlier studies linked damage within the SLF to disrupted connectivity and dysfunction within the fronto-parietal network resulting in behavioural deficits in spatial (egocentric) neglect (Bartolomeo et al., 2007; Corbetta et al., 2005; Corbetta and Shulman,

2002; Doricchi and Tomaiuolo, 2003; He et al., 2007; Karnath et al., 2009; Thiebaut de Schotten et al., 2008; Thiebaut de Schotten et al., 2005). In addition to these previous reports, our data suggest that the SLF supports interactions between functionally specialized cortical regions involved in attentional control across multiple sensory modalities. We provide evidence that functional disconnection resulting from SLF damage contributes to altered performance on attention tasks measuring not only spatial (egocentric) neglect but also visual and tactile extinction. Our data also indicate that lesions within the internal capsule/thalamic radiations and two other long association pathways (ILF and IFOF) were associated with different aspects of extinction. These findings are in agreement with previous studies investigating white matter disconnection in visuospatial attention disorders (e.g., Bird et al., 2006; Fimm et al., 2001; Urbanski et al., 2008). Furthermore, these results support the notion that visuospatial attention operates via large-scale cortical networks interconnected via several long-range pathways (Bartolomeo et al., 2007; Corbetta and Shulman, 2002; Mesulam, 1981). Finally, both lesions within SLF, with its fibers arching around the putamen (Catani et al., 2002; Nieuwenhuys et al., 1988), and lesions within the internal capsule, point to the potential role of direct anatomical connections between cortical regions and the basal ganglia in visuospatial selection.

Our conclusion here about the central role of the SLF in interconnecting attention networks is bolstered by a recent detailed DTI-fMRI report in healthy controls (Umarova et al., 2010). This elegant study used probabilistic tractography approach to investigate structural connectivity between neuronal substrates of attention identified based on functional imaging. The authors first identified cortical regions activated by a visuospatial attention task and then, using these as tractography seed points, they grouped probabilistic maps into the proposed visuospatial attention network. Interestingly, they found that this network consisted

of both dorsal (connecting temporoparietal with frontal regions) and ventral (travelling from temporoparietal regions towards insula and putamen) pathways. The dorsal pathways identified by Umarova et al. (2010) correspond to the SLF, which was identified by our study as the pathway supporting interactions between functionally specialized cortical regions involved in attentional control across multiple sensory modalities (thus causing variety of attention disorders when damaged). Although our study also indentified some ventral pathways and connection between cortical regions and the basal ganglia, these only loosely correspond to Umarova et al. (2010) findings. The ventral connections identified by Umarova et al. (2010) were assigned to the anterior part of IFOF and/or extreme/external capsule, while in our study we assigned as ventral connections more posterior part of IFOF, ILF and internal capsule.

Right hemisphere dominance and control of visuospatial attention: insights from extinction and neglect

Several studies have reported that spatial (egocentric) neglect and also visual extinction occur more frequently after right hemispheric damage, however while this phenomenon is widely accepted in the case of neglect, the evidence is weaker for visual extinction (e.g. Becker and Karnath, 2007; Cocchini et al., 1999; De Renzi et al., 1984; Pedersen et al., 1997; Ringman et al., 2004a; Stone et al., 1993). (Kinsbourne, 1977) and Mesulan (1981) propose that the asymmetry in the neglect syndrome reflects differential attentional biases in the two hemisphere - with the right hemisphere controlling shifts of attention to both the left and right sides of space and the left hemisphere only controlling shifts of attention to the right side (see Corbetta et al., 1993) for evidence from functional brain imaging). Alternative proposals are that right hemisphere dominance stems from the

contribution of non-spatial deficits to performance, such as right hemisphere dominance for alerting/arousal (Robertson et al., 1997a; Robertson et al., 1998) or from visual short-term memory (Malhotra et al., 2005). We did not set out to evaluate the clinical incidence of extinction after left and right hemisphere lesions, since our patients had chronic deficits and were selected on the basis of having a broad set of neuropsychological problems across the sample. Nevertheless it is interesting to note that there were no differences in the ratios of our patients showing or not showing a clinical deficit in visual or tactile extinction across groups with bilateral, unilateral left and unilateral right hemisphere lesions ($x^2<1.0$ and $x^2=2.56$, $p=0.278$ for visual and tactile extinction; see Table 4). The lesion analyses also indicate a striking similarity between neuronal substrates of left and right visual extinction and in particular demonstrate that the left and right TPJs are involved respectively with right and left-side extinction. To the extent that extinction reflects biases in spatial competition for selection, these data suggest that both left and right TPJ regions enter into the competition for selection, and there may be bilateral competition across these regions to determine selection. Unbalancing this competition, by selective damage to either left or right TPJ, can introduce a spatial bias into the competition and extinction results. Recently, Shulman et al. (2010) have provided contrasting evidence using functional brain imaging in normal participants. They found that stimulus-driven shifts of spatial attention to both sides of space, and activity associated with target detection, were associated with increased activation in the right relative to the left TPJ (amongst other regions). They proposed that there is right hemisphere dominance for stimulus-related attentional shifts and target detection in vision, across both sides of space. However, were the right TPJ alone responsible for bilateral detection of briefly presented stimuli, then we would not expect right-side extinction in patients with damage to the left TPJ. This was not the case here. Our results indicate that, even if the right TPJ is

dominant for detection across both sides of space, the left TPJ is necessary for supporting the detection of right side items. Following damage to the left TPJ detection (presumably modulated through the right TPJ) is biased to favour the contralesional field. Importantly, another recent fMRI study (Doricchi et al., 2010) provides evidence matching our results, supporting the role of both left and right TPJs, rather than right TPJ alone, in attentional orienting. The study clearly demonstrates (Doricchi et al., 2010) that the left TPJ is undeniably activated by stimulus driven orienting and that in the conventional invalid versus valid BOLD comparison (as, for example, used by Shulman et al., 2010), the activation of the left TPJ goes undetected because the left TPJ contains neuronal populations responding to invalid target as well as neuronal populations responding to valid targets. Subsequently, bilateral TPJ activation is manifested when invalid targets are compared to targets preceded by neutral cues. Thus Doricchi et al. (2010) presents key evidence congruent with our findings and conclusions.

Methodological considerations

It should be noted that our findings on the role of white matter tracts, specifically SLF, in visuospatial attention were largely based on analyses using cytoarchitectonic probabilistic maps (Bürgel et al., 2006). The main limitation of the Bürgel et al (2006) white matter atlas is that the mapping of fibre tracts was achieved through the realignment of coronal histological sections. This method favours visualising fibres that run parallel to the direction of the histological slice but is less suitable for visualising fibres that run orthogonally to the direction of the slice, like those composing the SLF. Thus the estimation of the SLF contributions to cognitive deficits was relatively conservative. Subsequently, this would simply mean that our findings were obtained using an atlas that is not biased toward the

detection of lesions to the SLF – thus, if anything, this conservative method provided an underestimation of the contribution of the lesions within longitudinal white matter fibres composing the SLF to visuospatial deficits.

Another important methodological point should be made in relation to the voxel-wise analysis of white matter lesions. Neuronal fibres may be damaged at several different points along a white matter tract and this can result in the same functional outcome (i.e. the same behavioural deficits). Thus voxel based analysis approaches may fail to detect such disconnections (Rudrauf et al., 2008b). Despite this non-optimised approach voxel based analysis can highlight functional disconnections when spatially overlapped. Hence the impact of neuronal disconnections on cognitive functioning needs to be carefully considered when drawing conclusions from lesion symptom studies (see Catani, 2007; Catani and Ffytche, 2005; Rudrauf et al., 2008b).

Conclusions

In summary our work indicates the central role of the temporo-parietal junction and the superior longitudinal fasciculus in supporting multi-item competition and attentional bias in visuospatial selection. We conclude that the TPJ in each hemisphere plays a role in the competitive interactions across space that determine the identification of multiple items, briefly presented across different modalities. In addition, the SLF seems necessary to support interaction between functionally specialized regions involved in attentional control across the varying sensory modalities.

Table 5. Grey matter substrates of visual extinction (VBM: Analysis 1).

Contrast	Cluster level		Voxel level			Coordinate			Brain Structure (location)
	P_{corr}	Size	P_{FWE}	P_{FDR}	Z-score	X	Y	Z	
Left unilateral bias									
	0.002	114	1.000	0.999	3.65	**6**	**-84**	**-6**	Right calcarine sulcus
Left visual extinction									
	0.000	6571	0.402	0.016	4.67	**60**	**-52**	**36**	Right IPL (SMG and angular gyrus), insula, STS, TPJ, MOG, MTG, MFG/IFG
	0.000	276	0.773	0.016	4.40	**24**	**20**	**-2**	Right putamen
Right unilateral bias									
	0.007	106	1.000	0.950	3.05	**-12**	**-94**	**-6**	Left calcarine sulcus
Right visual extinction									
	0.000	1158	0.221	0.039	4.84	**-42**	**-66**	**18**	Left IPL (SMG and angular gyrus), STS, TPJ, MTG, MOG
	0.000	275	0.532	0.040	4.58	**-14**	**-62**	**28**	Left precuneus

Abbreviations: IFG, inferior frontal gyrus; IPL, inferior parietal lobule; MFG, middle frontal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; SMG, supramarginal gyrus; STS, superior temporal sulcus; TPJ, temporo-parietal junction; VBM, voxel-based morphometry.

Table 6. White matter substrates of visual extinction (VBM: Analysis 1).

Contrast	Cluster level		Voxel level			Coordinates			Brain Structure (location)
	P_{corr}	Size	P_{FWE}	P_{FDR}	Z-score	X	Y	Z	
Left unilateral bias									
	0.000	1013	0.313	0.082	4.70	**20**	**-54**	**0**	Right optic radiation, IFOF, ILF
Left visual extinction									
	0.000	4663	0.000	0.000	6.26	**36**	**-46**	**30**	Right SLF, internal capsule (thalamic radiation), IFOF, ILF
Right unilateral bias									
	0.409	104	1.000	0.875	2.86	**-22**	**-64**	**-2**	Left IFOF
Right visual extinction									
	0.000	2150	0.030	0.015	5.19	**-20**	**-24**	**-2**	Left internal capsule (thalamic radiation), IFOF, ILF, SLF

Abbreviations: IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus; VBM, voxel-based morphometry.

Table 7. Grey matter substrates of visual extinction versus spatial neglect (VBM: Analysis 2).

Contrast	Cluster level		Voxel level				Coordinates			Brain Structure (location)
	P_{corr}	Size	P_{FWE}	P_{FDR}	Z-score	Inter* F(1,37)	X	Y	Z	
Left visual extinction*										
	0.000	1697	0.741	0.096	4.43	10.97	**38**	**-66**	**44**	Right angular gyrus, STS, insula, MOG
Left spatial neglect*										
	0.000	971	0.566	0.331	4.49	26.03	**46**	**-42**	**48**	Right SMG, intraparietal sulcus
	0.000	946	1.000	0.384	3.67	12.08	**36**	**18**	**-30**	Right STG extending to MTG
Common effect										
	0.000	196	0.550	0.004	4.57		**42**	**-10**	**58**	Right MFG/IFG
	0.000	1291	0.679	0.004	4.48		**66**	**-10**	**18**	Right TPJ, MTG, IPL
	0.000	175	0.991	0.006	4.08		**38**	**-56**	**46**	Right insula
	0.009	101	0.906	0.005	4.28		**24**	**6**	**-12**	Right putamen

* To further verify the observed dissociations between visual extinction and spatial neglect, we report here the results (F-tests) of the interaction analyses between the visual extinction and neglect, these analyses directly test whether brain-behaviour correlations observed for visual extinction are significantly higher than those observed for neglect, and vice versa.
Abbreviations: IFG, inferior frontal gyrus; IPL, inferior parietal lobule; MFG, middle frontal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; SMG, supramarginal gyrus; STG, superior temporal gyrus;STS, superior temporal sulcus; TPJ, temporo-parietal junction; VBM, voxel-based morphometry.

Table 8. White matter substrates of visual extinction versus spatial neglect (VBM: Analysis 2).

Contrast	Cluster level		Voxel level				Coordinates			Brain Structure (location)
	P_{corr}	Size	P_{FWE}	P_{FDR}	Z-score	Inter* F(1,37)	X	Y	Z	
Left visual extinction*										
	0.000	2977	0.002	0.000	5.65	15.91	**38**	**-44**	**32**	Right SLF, thalamic radiation, IFOF, ILF
Left spatial neglect*										
	0.000	964	0.000	0.000	5.94	57.92	**16**	**-12**	**-6**	Right internal capsule, sup thalamic radiation, IFOF
Common effect										
	0.000	923	0.052	0.000	5.09		**26**	**-26**	**44**	Right SLF
	0.000	276	0.000	0.000	6.10		**28**	**-24**	**2**	Right thalamic radiation

* To further verify the observed dissociations between visual extinction and spatial neglect, we report here the results (F-tests) of the interaction analyses between the visual extinction and neglect, these analyses directly test whether brain-behaviour correlations observed for visual extinction are significantly higher than those observed for neglect, and vice versa.
Abbreviations: IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus; sup, superior; VBM, voxel-based morphometry.

Table 9. Grey matter substrates of visual versus tactile extinction (VBM: Analysis 3).

Contrast	Cluster level		Voxel level				Coordinates			Brain Structure (location)
	P_{corr}	Size	P_{FWE}	P_{FDR}	Z-score	Inter* F(1,35)	X	Y	Z	
Left visual extinction*										
	0.000	1051	0.237	0.032	4.83	20.86	**42**	**-68**	**42**	Right angular gyrus, STS, MTG, MOG
Left tactile extinction*										
	0.000	289	0.510	0.147	4.61	25.83	**26**	**-4**	**-6**	Right putamen
	0.000	266	0.783	0.147	4.42	21.03	**56**	**-12**	**48**	Right postcentral gyrus
Common effect										
	0.000	523	0.817	0.006	4.39		**56**	**-26**	**12**	Right TPJ

* To further verify the observed dissociations between visual and tactile extinction, we report here the results (F-tests) of the interaction analyses between the visual and tactile extinction, these analyses directly test whether brain-behaviour correlations observed for visual extinction are significantly higher than those observed for tactile extinction, and vice versa.
Abbreviations: MOG, middle occipital gyrus; MTG, middle temporal gyrus; STS, superior temporal sulcus; TPJ, temporo-parietal junction; VBM, voxel-based morphometry.

Table 10. White matter substrates of visual versus tactile extinction (VBM: Analysis 3)

Contrast	Cluster level		Voxel level				Coordinates			Brain Structure (location)
	P_{corr}	Size	P_{FWE}	P_{FDR}	Z-score	Inter* F(1,35)	X	Y	Z	
Left visual extinction*										
	0.000	3703	0.080	0.002	5.01	17.16	**36**	**-60**	**26**	Right SLF, thalamic radiation, IFOF
Left tactile extinction*										
	0.000	732	1.000	1.000	3.30	8.22	**22**	**-24**	**-2**	Right internal capsule, ILF
Common effect										
	0.000	342	0.229	0.002	4.80		**34**	**-46**	**32**	Right SLF

* To further verify the observed dissociations between visual and tactile extinction, we report here the results (F-tests) of the interaction analyses between the visual and tactile extinction, these analyses directly test whether brain-behaviour correlations observed for visual extinction are significantly higher than those observed for tactile extinction, and vice versa.
Abbreviations: IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus; VBM; voxel-based morphometry.

CHAPTER 4:

THE NEURAL UNDERPINNINGS OF SIMULTANAGNOSIA: DISCONNECTING THE VISUOSPATIAL ATTENTION NETWORK[12]

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ABSTRACT

Due to our limited processing capacity, different elements of the visual scene compete for the allocation of processing resources. One of the most striking deficits in visual selection is simultanagnosia, a rare neuropsychological condition characterized by impaired spatial awareness of more than one object at time. To decompose the neuroanatomical substrates of the syndrome and to gain insights into the structural and functional organization of visuospatial attention, we performed a systematic evaluation of lesion patterns in a group of simultanagnosic patients compared to patients with either (i) unilateral visuospatial deficits (neglect and/or extinction) or (ii) bilateral posterior lesions without visuospatial deficits, using overlap/subtraction analyses, estimation of lesion volume and a lesion laterality index. We next used voxel-based morphometry (VBM) to assess the link between different visuospatial deficits and grey and white matter damage. Lesion overlap/subtraction analyses, lesion laterality index and VBM measures converged to indicate that bilateral parieto-occipital white matter disconnections are both distinctive and necessary to create symptoms associated with simultanagnosia. We also found that bilateral grey matter damage within the middle frontal area (BA46), cuneus, calacarine and parieto-occipital fissure as well as right hemisphere parietal lesions within intraparietal and postcentral gyri were associated with simultanagnosia. Further analysis of the white matter based on tractography revealed associations with bilateral damage to major pathways within the visuospatial attention network, including the superior longitudinal fasciculus, the inferior fronto-occipital fasciculus and the inferior longitudinal fasciculus. We conclude that damage to the parieto-occipital regions and the intraparietal sulcus, together, with bilateral white matter disconnections within the visuosptial attention network, contribute to poor visual processing of multiple objects and the loss of processing speed characteristic of simultanagnosia.

INTRODUCTION

Visual attention provides us with the ability to select and process a subset of behaviourally relevant visual stimuli while ignoring the rest of visual scene. Within a visual display many different elements strive for neural representation and the allocation of processing resources. The process of forming neural representations for these elements is competitive due to our limited processing capacity and the need to ensure that behaviourally relevant information gets priority. Functional models of visual attention stress the competition for selection and the modulating role of both bottom-up salience and behavioural prioritization in this process (Bundesen, 1990; Duncan and Humphreys, 1989). Data on the neural underpinnings of the selection system come from both single unit recordings and functional neuroimaging studies, which converge to highlight the critical role of a frontoparietal network in mediating the selection of specific visual locations. Evidence on the necessary role of these regions comes also from lesion-symptom mapping studies of patients with various visual and spatial attention deficits (e.g., Chechlacz, 2010; Karnath et al., 2004; Medina et al., 2009; Mort et al., 2003; Verdon et al., 2010). One particularly interesting disorder is simultanagnosia, a rare neuropsychological condition characterized by impaired spatial awareness of more than one object at time (Bálint, 1909; Rizzo and Vecera, 2002).

Simultanagnosia provides a unique opportunity to study the nature of human visuospatial processing as it reflects a (largely) non-lateralised deficit in selecting multiple objects (Dalrymple et al., 2011; Riddoch et al., 2010; Rizzo and Vecera, 2002; Robertson et al., 1997b). Wolpert (1924) described simultanagnosia as an inability to interpret a complex visual scene (processing multiple items and the relations between them), despite preservation of the ability to apprehend individual items. Simultanagnosia has also been associated with deficits in global processing (Jackson et al., 2004; Karnath et al., 2000; Shalev et al., 2005;

Shalev et al., 2007), though studies have also demonstrated that global processing may take place implicitly (Jackson et al., 2004; Karnath et al., 2000; Shalev et al., 2005); see also Demeyere et al., 2008). In detailed attempts to assess simultanagnosia in relation to formal accounts of attention e.g., using the Theory of Visual Attention (TVA; Bundesen, 1990), Duncan et al. (1999, 2003) argued that a deficit in the rate of visual processing might be critical, over and above problems in visual short-term memory or biases in spatial selection. This slowing of information processing could reflect impaired sub-cortical pathways over and above damage to cortical regions. Therefore, understanding the extent and detailed location of sub-cortical disconnections in simultanagnosia, may provide key insights into not only the neuropathology of simultanagnosia but also the necessary role of structural connections within the visuospatial attention network.

Simultanagnosia leading to poor scene interpretation has been reported primarily in patients with bilateral parietal (e.g. Clavagnier et al., 2006) and occipital lesions (Rizzo and Hurtig, 1987; see Rizzo and Vecera, 2002 for a review). There have also been some documented cases following either left or right unilateral parietal brain damage (Clavagnier et al., 2006; Karpov et al., 1979; Naccache et al., 2000) but at least in some of these unilateral cases (Clavagnier et al., 2006; Naccache et al., 2000) the lesions have included damage to the corpus callosum, consistent with impaired interhemispheric transfer of visual information. Notably, current understanding of simultanagnosia has been limited largely to case studies, making it difficult to fully assess and decompose the underlying neuronal substrates.

Simultanagnosia can also co-occur with visual neglect and extinction, noted from Bálint's (1909) original case onwards, but previous work fails to specify the neuroanatomical relationship between simultanagnosia and other associated visuospatial disorders (see Rizzo and Vecera, 2002). The areas of damage in these syndromes seem to overlap, both within the

cortex (e.g., damage within the angular gyrus has been reported in both neglect and simultanagnosia; Chechlacz et al., 2010 [Chapter2]; Hillis et al., 2005; Mort et al., 2003; Rizzo and Vecera, 2002) and sub-cortically (Bartolomeo et al., 2007; Riddoch et al., 2010). Understanding common and distinct patterns of lesions in patients with different visuospatial deficits could potentially contribute to understanding organization and functional specialization within the visuospatial attention network.

To provide a neuroanatomical analysis of simultanagnosia, we first performed a systematic evaluation of lesion patterns in a group of patients suffering from the disorder. The lesion distribution in this group of patients was next compared to patterns of lesions in two groups of 'control' patients with i) either left or right unilateral visuospatial attention deficits (neglect and/or extinction) and ii) bilateral posterior lesions but without any visuospatial deficits. In addition, lesion patterns in simultanagnosia patients were compared with lesions in a sample of consecutive patients admitted to the Behavioural Brain Sciences Centre at Birmingham University with the presence of a variety of neuropsychological symptoms and who were not pre-selected based on any anatomical criteria. The integrity of grey and white matter was evaluated using advanced MRI sequences: high resolution T1, T2 FLAIR and diffusion tensor imaging (DTI). To provide converging evidence for the structure-function relationships we analysed the data using lesion overlap and subtraction methods and also employed whole brain statistical analyses (voxel-based morphometry VBM; Ashburner and Friston, 2000) to assess the link between visuospatial deficits and grey and white matter damage. To test the hypothesis that bilateral disconnections contribute to the symptoms of simultanagnosia, we computed a laterality index based on lesion volume and lesion location. Finally, to test the hypothesis that simultanagnosia symptoms are associated with neuroanatomical disconnection, we used a streamline tractography approach to specifically

evaluate the integrity of white matter pathways that are known to be associated with visual processing and spatial awareness connecting the occipital, parietal and frontal cortices: the superior longitudinal fasciculus (SLF), the inferior longitudinal fasciculus (ILF) and inferior fronto-occipital fasciculus (IFOF). The current study differs from earlier reports in terms of sample size and data analysis methods. Previous studies were typically based on a single case reports, by contrast we based our findings on a group of seven patients, which provides the basis for more detailed anatomical analyses. Simultanagnosia remains a rare condition and while a group of seven patients represents a substantially large sample size for such condition, the size of the sample itself presents some limitations. Therefore, as described above, the present study aimed to employ and contrast different neuroimaging methods in order to draw converging conclusions about anatomical substrates of simultanagnosia, and not to reflect a particular data analysis method.

The results are discussed in relation to the anatomical dissociations between simultanagnosia and unilateral visuospatial attention deficits, as well as the functional organization of the interconnected networks underlying visuospatial attention. We conclude that our lesion-symptom mapping findings advance our understanding of the functional underpinnings of simultanagnosia, which at a functional level, are consistent with Duncan et al.'s (2003) argument linking simultanagnosia to severe impairments in visual processing speed.

METHODS

Participants

Patients. Fifty-nine patients participated (43 males and 16 females), with ages ranging from 20 to 85 years (mean age 61.1 years), and were divided into experimental and control

groups. All patients had acquired brain lesions (stroke, vasculitis, degenerative changes), were at a chronic stage (> 9 months post injury) and had no contraindications to MRI scanning. No other exclusion criteria were used. All the patients were recruited from the panel of neuropsychological volunteers established in the Behavioural Brain Sciences Centre at the School of Psychology, University of Birmingham. All patients provided written informed consent in agreement with ethics protocols at the School of Psychology and Birmingham University Imaging Centre.

Table 11. Patients' details: clinical and demographic data (all 59 patients)

	Simultanagnosia (SM) **(n=7; *n=5)**	**Controls** **(n=52)**
Mean age in years (SD)	62.7 ±7.7 (*61.6 ±9.2)	61.3 ±14.5
Sex	3 females, 4 males (*2 females, 3 males)	13 females, 39 males
Aetiology	5 stroke, 2 CBD (*4 stroke, 1 CBD)	49 stroke, 1 CBD, 2 HSE
Lesion side	7 bilateral (*5 bilateral)	14 bilateral, 13 left, 25 right
Mean time post lesion in years (SD)	6.7 ±6.7 (*5.0 ±5.6)	4.9 ±5.0
Simultanagnosia	7 (*5)	0
Allocentric Neglect	5 left (*3 left)	8 left, 1 right
Egocentric Neglect	3left, 2 right (*1 left, 2 right)	6 left, 4 right
Visual extinction	7 left (*5 left)	13 left, 8 right
Visual field defects	1 left	2 left, 3 right

CBD = cortico-basal degeneration; HSE = herpes simplex encephalitis; *as we were unable to obtain DTI data for all simultanagnosic patients, the asterisk and numbers in brackets indicate clinical and demographic data for patients who underwent DTI scan;

Table 12. Patient details: clinical and demographic data (patients selected for lesion overlap/subtraction analyses)

	SM (n=7)	LVS controls (n=7)	RVS controls (n=7)	Bilateral controls (n=7)
Mean age in years (SD)	62.7 ±7.7	67.3 ±8.5	67.3 ±14.7	65.4 ±13.7
Sex	3 females	7 males	1 female	2 female
	4 males		6 males	5 males
Aetiology	5 stroke	7 stroke	7 stroke	5 stroke
	2 CBD			2 HSE
Lesion side	7 bilateral	7 right	7 left	7 bilateral
Mean time post lesion in years (SD)	6.7 ±6.7	4.9 ±3.5	4.6 ±3.4	10 ±7.8
Simultanagnosia	7	0	0	0
Allocentric Neglect	5 left	4 left	2 right	0
Egocentric Neglect	5 = 3 left, 2 right	4 left	2 right	0
Visual extinction	7 left	4 left	5 right	0
Visual field defects	1 left	1 left	1 right	0

CBD = cortico-basal degeneration; HSE = herpes simplex encephalitis; LVS = left visuospatial deficits; RVS= right visuospatial deficits; SM = simultanagnosia

The experimental group consisted of seven patients with simultanagnosia (SM). All of these patients also had either neglect or visual extinction, with their problem in visuospatial processing tending to be worse on one side (typically the left). For the purpose of lesion subtraction analyses three different matched control groups were used: i) patients with a unilateral lesion and contralateral visuospatial deficits, either neglect and/or extinction (seven with left and seven with right-side deficits; groups LVS and RVS, respectively) and ii) seven patients with bilateral parietal and/or occipital lesions but without visuospatial deficits (Bilat group; these patients were selected based on presence of bilateral posterior lesions within either parietal or occipital cortices). For the VBM analyses, an unbiased sample of fifty-two

chronic neurological patients who did not show any of simulatanagnosia symptoms served as the control group. Note that this group included 27 patients with some degree of visuospatial deficit (15 with left and 12 with right-side deficits). See Tables 11-12 for full clinical and demographic data.

Healthy Controls. For the lesion identification protocol (see below) we acquired T1-weighted images from 100 healthy controls (55 males and 45 females, mean age 54.5 years, range 20-87) with no history of stroke, brain damage or neurological disorders. We also acquired control data set from 20 healthy control participants (13 males and 7 females, mean age 60.5 years) for DTI-tractography. All controls provided written informed consent in agreement with ethics protocols at the School of Psychology and Birmingham University Imaging Centre.

Behavioural measures

Simultanagnosia assessment. Simultanagnosia was diagnosed as a clinical deficit in reporting the gist of a scene shown for at least 2s, which is more than sufficient for control participants to realise the scene's gist (see below; if necessary patients were given unlimited time until it was clear that the patient was unable to report the gist and that any problems were not due to naming difficulties, slow or slurred speech etc). There were 8 black and white line drawings of scenes from everyday life and the scenes were chosen so that the gist could be gained from the information on either the left or right of the scenes and thus the problems in understanding the gist should not be due to a lateralised deficits; the diagnosis was based on the evaluation whether patients were able to interpret the overall meaning of the scene/gist or only reported isolated single items. In addition simultanagnosia was diagnosed as a clinical deficit based on the duration required to achieve successful report of 2 letters (each 0.5deg)

presented using E-Prime software (Psychology Software Tools), each centred 2 deg from fixation (1 above, 1 below, to minimise unilateral spatial deficits; see Kinsbourne and Warrington, 1962). Performance on this task was also assessed in 10 age-matched controls. None of the controls had difficulty in describing the gist of the scenes at the presentation durations used and all were able to report two letters shown for 50ms. Patients were classed as having simultanagnosia if they both made errors on at least 3/8 scenes and if they required letter presentations of 200ms or more to report both letters. Where patients had naming difficulties, semantic circumlocutions that described the nature of the scenes were counted as correct.

Visuospatial Attention Battery. In order to measure the visuospatial deficits of egocentric neglect, allocentric neglect and visual extinction, we carried out cognitive assessment with a battery of tests from Birmingham University Cognitive Screen (BUCS) including Apple Cancellation and Visual Extinction Tests. Full details of the tests are available online at http://www.bucs.bham.ac.uk. The diagnosis of neglect was based on Apple Cancellation task, which is similar to the gap detection task by Ota et al. (2001) and is designed to simultaneously measure allocentric and egocentric neglect (see Chechlacz et al., 2010 [Chapter 2], Bickerton et al., 2011). Patients were classed as having a clinical deficit on measures of egocentric and allocentric neglect and visual extinction if their scores on the Apple and Visual Extinction tests fell outside the norms for the tests taken from 86 control participants with no history of neurological diseases (35 males and 51 females, mean age 67 years, range 47-88). Furthermore, for clear-cut diagnosis of visual extinction we additionally used a computer task consisting of 48 single item and 48 bilateral letter detection trials. For full details see Supplementary Material (Appendix 3). Control norms for visual extinction computer test were assessed based on performance of 10 control participants with no history

of neurological diseases and no lesions on MRI scans (5 males and 5 females, age range 62-74). Cut-offs to classify patients as having visual extinction were calculated on the basis of bilateral asymmetry scores (left vs. right-side errors). Control participants made a maximum of two errors on a single side or both sides and therefore the asymmetry scores >2 were classified as abnormal. Patients were classified as having visual extinction if they fulfilled criteria of at least one of the tests.

Neuroimaging assessment

Patients and healthy controls were scanned at the Birmingham University Imaging Centre (BUIC) on a 3T Philips Achieva MRI system with 8-channel phased array SENSE head coil. Patients' scans were obtained in close proximity to the time of behavioural testing. The anatomical scan was acquired using a sagittal T1-weighted sequence (sagittal orientation, TE/TR=3.8/8.4ms, voxel size 1x1x1mm^3) and for 49 patients we were able to acquire an additional T2 FLAIR sequence (TR=11000ms, TE=125ms, voxel size 0.45x0.44x2 mm^3). We acquired DTI data for 25 healthy controls and 5 patients with simultanagnosia employing echo plannar imaging (64 slices with isotropic 2x2x2 mm^3 voxels, TR=6170ms, TE=78ms). DTI was acquired in 61 gradient directions with a b value of 1500s/mm^2 and 1 volume was acquired with no diffusion weighting (b=0 image).

Image pre-processing

T1 scans from patients and healthy controls were first converted and reoriented using MRICro (Chris Rorden, Georgia Tech, Atlanta, GA, USA). Pre-processing was done in SPM5 (Statistical Parametric Mapping, Welcome Department of Cognitive Neurology, London UK). The brain scans were transformed into the standard MNI space using the unified-segmentation procedure (Ashburner and Friston, 2005). The unified-segmentation procedure involves tissue

classification based on the signal intensity in each voxel and on a-priori knowledge of the expected localization of grey matter (GM), white matter (WM), cerebrospinal fluid (CSF) in the brain. To further improve tissue classification and spatial normalization of lesioned brains we used a modified segmentation procedure (Seghier et al., 2008). This protocol was developed to resolve problems with misclassification of damaged tissue by including an additional prior for an atypical tissue class (an added "extra" class) to account for the "abnormal" voxels within lesions and thus allowing classification of the outlier voxels (Seghier et al., 2008). While earlier versions of SPM struggled with normalizing and segmenting brains containing large lesions (e.g. Stamatakis and Tyler, 2005) the unified-segment procedure as implemented in SPM5 has been shown to be optimal for spatial normalization of lesioned brains (Crinion et al., 2007). Following segmentation, we visually inspected each of the segmented scans to assess whether segmentation and normalisation was successful. Finally, the segmented images were smoothed with a 8 mm FWHM Gaussian filter to accommodate the assumption of random field theory used in the statistical analysis (Worsley, 2003). The choice of intermediate smoothing of 8mm FWHM was previously shown to be optimal for lesion detection and further analysis of segmented images (e.g. Leff et al., 2009; Seghier et al., 2008; Stamatakis and Tyler, 2005). The pre-processed GM and WM images were used for automated lesion identification using fuzzy clustering (Seghier et al., 2008) and in the voxel-based analyses to determine the relationships between lesion site and simultanagnosia.

Lesion Mapping and Analysis

Automated lesion identification. Lesion maps from individual patients were reconstructed using a modified segmentation procedure (see above) and an outlier detection

algorithm based on fuzzy clustering (for a description of the full procedure including validation based on real and simulated lesions on T1-weighted scans, see Seghier et al., 2008). This procedure identifies voxels that are different in the lesioned brain as compared to a set of healthy controls (here we employed a set of 100 healthy controls as described above) using normalised grey and white matter segments. The GM and WM outlier voxels are then combined into a single outlier image and thresholded to generate a binary map of the lesion (Seghier et al., 2008). The results of lesion reconstruction were verified against each patient's T1 and T2 FLAIR scans. The anatomical localization of the lesion sites for patients with simultanagnosia was based on the Duvernoy Human Brain Atlas (Duvernoy et al., 1991) and the Woolsey Brain Atlas (Woolsey et al., 2008). The lesion volumes for each patient were calculated using Matlab 7.5 (The MathWorks, Natick, MA, USA) based on binary lesion maps. Subsequently we applied GM and WM masks defined using the WFU Pick atlas software toolbox in conjunction with SPM5 (Maldjian et al., 2003) to calculate GM and WM lesion volumes for each patient.

Lesion overlaps and subtractions. The lesion comparisons across patients were done with SPM5 using *Image Calculator* functions. To estimate lesion overlap within the experimental groups (SM), a single colour set was used with colours ranging from dark to light, coding values representing the number of patients having a lesion to a particular brain area. To estimate differences in lesion location (i.e. to calculate brain regions that were lesioned in one group of patients but spared in other group), subtraction plots were computed. The lesion subtraction plots use two different colour sets (one for positive and one for negative values) with colours ranging from dark to light, coding increasing frequencies. Subtraction analyses were computed for the following groups: 1) SM vs. LVS; 2) SM vs RVS and 3) SM vs Bilat. The results were displayed using MRIcron.

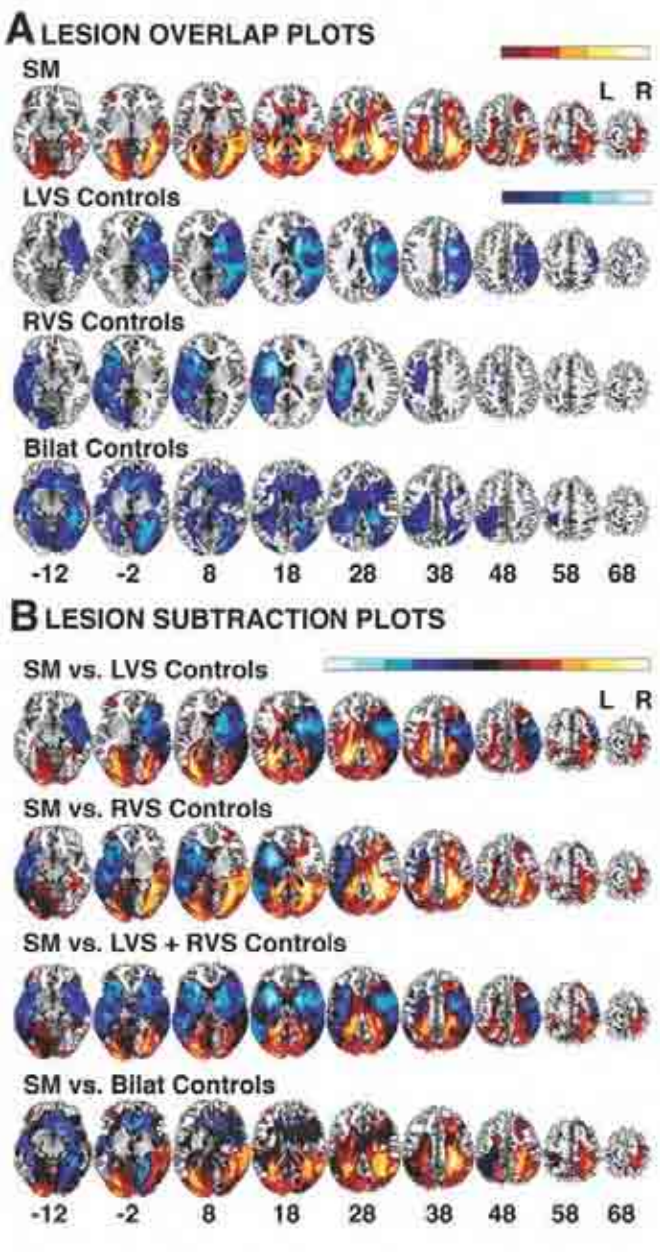

Figure 12. (A) Lesion overlap plots for simultanagosic patients (SM, n=7) and three control groups without any simultanagnosia symptoms: patients with left visuospatial deficits and right brain lesions (LVS controls, n=7), patients with right visuospatial deficits and left brain lesions (RVS controls, n=7) and patients with bilateral fronto-parieto-occipital lesions but with neither neglect nor extinction (Bilat controls, n=7). The colour range indicates the number of patients with overlapping lesions, from brown (n=1) to light yellow (n=7) for the simultanagnosic group (SM) and from dark blue (n=1) to pale blue (n=7) for all control groups. **(B)** Lesion subtraction plots for SM patients vs different control groups as listed above. On subtraction plots warm colours (brown to light yellow) represent brain regions damaged more frequently in patients with simultanagnosia relative to different control groups represented by cold colours (dark blue to pale blue). Note that black (middle of the colour bar) indicates regions where the frequency of damage is identical in both groups. The lesion overlap and subtraction plots are presented as an overlay on a standard T1 multi-slice

template in MRIcron (Chris Rorden, Georgia Tech, Atlanta, GA, USA). MNI z-coordinates of the axial sections are given. All images are displayed in neurological convention i.e. left of the slice represents the left hemisphere.

Voxel-based morphometry (VBM)

Overlap/subtraction analyses involve calculating the number or proportion of patients with damage within a specific region based on selecting groups (typically matched in size) of patients with or without specific behavioural deficits. These traditional lesion overlap/subtraction methods may be insufficient to precisely identify brain-behaviour relationship due to both behavioural (small sample) and anatomical biases. These methods also do not control for the effects of potentially co-varying factors, such as age, time since lesion and lesion volume that could affect cognitive performance. More importantly these methods do not take into account variability between patients and hence cannot assess the reliability of the observations. Such limitations can be overcome by using more robust statistical analyses carried out without prior patient selection. Therefore to complement our lesion overlap/subtraction analysis, we next applied a voxel-wise statistical approach to assess the link between the cognitive deficits in simultanagnosia and brain damage using normalized and smoothed GM and WM images.

To assess the relationship between WM and GM damage and simultanagnosia on a voxel-by voxel basis, we used a VBM approach (Ashburner and Friston, 2000) and carried out statistical analyses with SPM5 using smoothed GM and WM maps obtained from segmented scans from our patient sample (see above for the pre-processing protocol). We used parametric statistics within the framework of the general linear model (Kiebel and Holmes, 2003) and the analyses for WM and GM were carried out separately. In each statistical model age, handedness, gender, type of lesion, time since diagnosis and lesion volume were included as covariates of no interest. All these covariates ensured that we could

control for various confounding factors that potentially might have affected cognitive performance. The analyses included all 59 patients (see above and Table 1 for details). In our analyses we asked three questions: 1) what are the neural correlates of simultanagnosia? (*Analysis 1* comparing 7 SM patients to the unbiased sample of 52 patients); 2) what is the relationship between the neuronal substrates of simultanagnosia and left visuospatial deficits (*Analysis 2*)? and 3) what is the relationship between the neuronal substrates of simultanagnosia and right visuospatial deficits (*Analysis 3*)? *Analysis 2* and *3* aimed to formally test for common and dissociated neuronal substrates that contribute to simultanagnosia and other common visuospatial deficits such as egocentric neglect, allocentric neglect and visual extinction. Dissociating simultanagnosia from either left visuospatial deficits or right visuospatial deficits was achieved by using exclusive masking, i.e. testing for a change in voxel intensity that correlated with simultanagnosia ($p < 0.001$, uncorrected) but not with either left or right visuospatial deficits ($p > 0.05$, uncorrected). Common mechanisms were tested by using an inclusive mask - i.e. selecting all voxels common to both simultanagnosia and either left or right visuospatial deicits. We report only results that showed significant effect at $p< 0.001$ FWE-corrected threshold at the cluster level with amplitude of voxels surviving $p< 0.001$ uncorrected across the whole brain and an extent threshold of 200mm^3 (>100 voxels). The brain coordinates are presented in standardized MNI space. The anatomical localization of the lesion sites within the grey matter was based on the Anatomical Automatic Labeling toolbox (AAL toolbox, Tzourio-Mazoyer et al., 2002), the Duvernoy Human Brain Atlas (Duvernoy et al., 1991) and the Woolsey Brain Atlas (Woolsey et al., 2008). In order to localize white matter lesions associated with visual extinction in relation to specific white matter pathways we used the JHU White matter tractography atlas

(Hua et al., 2008) and the MRI Atlas of Human White Matter (Mori, 2005). The brain coordinates are presented in the standardized MNI space.

Lesion volume and laterality index. In addition to the VBM analyses we tested whether simultanagnosia is simply associated with larger lesion volume compared to the control patients (i.e. 14 SM vs. 14 unilateral VS + 7 Bilat). Next, to assess whether the symptoms are predominantly related to white matter disconnection, we compared lesion volume of the GM and WM. A mixed-design ANOVA was used with patient groups (7 SM vs. 14 unilateral VS + 7 Bilat) as the between-participants factor and lesion volume (GM vs. WM lesion volume) as the within-participants factor. Finally simultanagnosia symptoms have been reported in patients with predominantly bilateral lesions. To test how crucial bilateral occipito-parietal lesions are to the simultanagnosia syndrome, we computed a lesion laterality index based on the lesion volume in the different lobes. The brain region encompassing each lobe was defined using the WFU Pick atlas software toolbox in conjunction with SPM5 (Maldjian et al., 2003). We then calculated a lesion laterality index (i.e. (left - right) / (left+right)) separately for the GW and WM lesions within the frontal, temporal and parieto-occipital lobes. The reliability of differences between the patient groups: SM vs Bilat was computed using a two-sample t-test. We used Matlab 7.5 (The MathWorks, Natick, MA, USA) and SPSS16 (SPSS, Chicago, IL, USA) for the statistical analyses.

Image analyses: DTI data

Data processing. All DTI data sets were first converted using dcm2nii (Chris Rorden, Georgia Tech, Atlanta, GA, USA) and then analysed using FSL (FMRIB, Oxford UK). First all raw data were corrected for distortions due to eddy currents and any movements using FSL eddy correction module within FSL FDT toolbox (Smith et al., 2004).

DTI tractography: We detected and quantified the extent and laterality of damage within the superior longitudinal, inferior longitudinal and inferior fronto-occipital fasciculi based on tractography and tract-specific measures. For the purpose of this analysis we used the DTI data available for 5 patients with simultanagnosia (ages range from 47 to 71 years; mean age 61.6 years ± 9.2 years; 2 females, 3 males) and for comparison we included DTI data obtained for 20 healthy controls (ages range from 45 to 74 years; mean age 60.5 years ± 9.2 years; 7 females, 13 males). For comparison we also included in the analysis data from 5 patients with left visuospatial deficits and right brain lesions (LVS, ages range from 53 to 76 years; mean age 64.8 years ± 8.6; years; 5 males), 5 patients with right visuospatial deficits and left brain lesions (RVS, ages range from 54 to 81 years; mean age 65.2 years ± 10.3 years; 1 female, 4 males), 7 chronic neurological patients without any visuospatial deficits with either bilateral (n=3) or left (n=2) or right (n=2) brain lesions (CN, ages range from 40 to 72 years; mean age 54.6 years ± 10.7 years; 3 females, 4 males). Tract reconstruction was performed using Diffusion Toolkit, followed by tract visualization and tract extraction using Trackvis (both programs developed by Ruopeng Wang, Van J. Wedeen, TrackVis.org, Martinos Center for Biomedical Imaging, Massachusetts General Hospital). For tract reconstruction we used the Fiber Assignment by Continuous Tracking (FACT) algorithm (Mori et al., 1999) as implemented in Diffusion Toolkit. Tracts were propagated along the direction of the primary eigenvector with tracking stopped when either the FA threshold was not met (FA value was lower than 0.15) or by the angle threshold exceeding 45 degree. The fibre tracking was first performed from every voxel in the brain and then followed by tract extraction using ROI filters. For extraction of the superior longitudinal fasciculus (SLF) a single ROI approach was used, while for the inferior longitudinal fasciculus (ILF) and inferior fronto-occipital fasciculus (IFOF) two ROI approaches were used based on the method

proposed by Mori (Mori et al., 2002), replicated by other research groups (e.g. Singh et al., 2010; Thomas et al., 2009). All tracts were extracted in native diffusion space by one of the authors (M.C.) using systematic protocols created and followed to ensure extraction consistency between participants (for full protocols see Supplementary Methods and Supplementary Figure 3, Appendix 3). We first compared the results of tract reconstruction for each patient with lesion location on a T1-weighted image. Subsequently, the trajectory of each reconstructed tract (in both patients and controls) was checked to ensure consistency with previous studies and neuroanatomical atlases (Catani et al., 2002; Catani and Thiebaut de Schotten, 2008; Mori et al., 2002) and the number of streamlines[13] for each tract as well as for the whole brain was calculated for all participants. The number of streamlines for the whole brain was used to estimate the overall extent of white matter damage in individual patients compared to controls. The total number of streamlines reflects individual differences in brain size and is often used to normalize the results for each tract of interest, however due to brain lesions in patients (but not in controls) this approach was not applicable in our study. The reliability of differences in the number of reconstructed streamlines between patients and the healthy controls as well as between various groups of patients was computed using a two-sample t-test. We used Matlab 7.5 (The MathWorks, Natick, MA, USA).

RESULTS

Behavioural Measures. Seven patients were diagnosed with simultanagnosia symptoms. All seven simultanagnosic patients were also diagnosed with left visual extinction. Two of these seven patients suffered from left allocentric and left egocentric neglect, while one had right

[13] Streamline or deterministic tractography allows reconstruction of major fiber bundles based on mathematical streamline algorithms used to interpolate fiber orientation (e.g., used here FACT algorithm; Mori et al., 1999). Such an approach results in a set of 3D curves representing “continuouos” pathways throughout DTI data set, which are visualized as cylindrical 3D tubes i.e. streamlines.

egocentric and left allocentric neglect. Two patients had left allocentric but not egocentric neglect, while one patient had left egocentric but not allocentric neglect (see Table 11). Control patients did not have any simultnangnosia symptoms but several patients suffered from unilateral visuospatial deficits, including eight patients with left and one with right allocentric neglect, six patients with left and four with right egocentric neglect and thirteen patients with left and eight with right visual extinction (see Table 11).

Neuroimaging Results

Lesion overlap and subtraction analyses. We first performed a systematic evaluation of lesion patterns in a group of simultanagnosic (SM) patients based on lesion overlap. The analysis revealed wide bilateral lesion overlap within white matter areas and less extensive overlap within grey matter. Specifically, we found large overlap in the white matter areas with maximal lesion overlap (seven out of seven SM patients) within bilateral inferior parietal, parieto-occipital and occipital lobes (suggesting damage to association and commissural pathways such as superior longitudinal fasciculus, posterior corona radiata, posterior thalamic radiation, inferior fronto-occipital, inferior longitudinal fasciculus and corpus callosum; Figure 12A top panel). Furthermore, SM patients had bilateral lesions in the grey matter areas of the frontal, parietal and occipital cortices, though the actual region of maximal overlap (four out of seven SM patients) was restricted to the bilateral cuneus, medial part of parieto-occipital fissure, right and to the lesser extent also left middle frontal area (BA46 i.e. middle frontal and inferior frontal gyri) and right inferior parietal lobule including portions of the angular and postcentral gyri (Figure 12A top panel).

Overall, the above findings suggest that simultanagnosia symptoms are associated with bilateral lesions to regions in the vicinity of the posterior parietal-occipital and middle frontal cortices. However, not all patients with bilateral lesions to these regions necessarily exhibit

simultanagnosic symptoms or indeed any spatial attention deficits (e.g. Bilat Controls, see bottom panel of Figure 12A). To test which lesions are critically associated with simultanagnosia, we contrasted lesion patterns in the SM group with the Bilat patient group using lesion subtraction analysis. We also compared the lesion pattern in the SM patients with that in patients with unilateral visuospatial deficits only (neglect and extinction – the LVS and RVS groups, see middle panels in Figure 12A), to separate the neuronal substrates commonly associated with neglect and extinction from those areas specifically associated with simultanagnosia. The subtraction plots showed that bilateral damage in the white matter within posterior parietal, parieto-occipital and occipital lobes were associated with simultanagnosia but these regions were spared in the control groups (Figure 12B). Moreover the subtraction plots also demonstrated that bilateral damage in the grey matter within the cuneus, parieto-occipital fissure, precuneus and right parietal cortex (including portions of the postcentral and intraparietal gyri) were associated with simultanagnosia but these regions were spared in all control groups (Figure 12B) Although, we also found overlap across some areas of damage within both grey and white matter in patients with simultanagnosia, extinction and neglect (in particular within inferior parietal lobule including the angular gurus), the subtraction plots clearly show that at least some of the anatomical substrates of simultanagnosia (SM) are separate from those characterising the other syndromes and, crucially, are bilateral.

Next we tested whether simultanagnosia is associated with wider spread lesions. We first compared overall lesion volume between the SM patients and those belonging to the three control groups (Bilat + LVS + RVS). On average lesion volume for the simultanagnosia patients was 47.39±20.35mm^3 (average ± sdev) and lesion volume in the control patients was 39.96 ±34.58mm^3 (Bilat=49.27±36.22mm^3, LVS=45.29±41.90mm^3, RVS=25.32±23.12

mm^3). Overall lesion volume in the simultanagnosia group was not significantly larger than in the other neuropsychological patients ($t(26)=0.54$, $p>0.5$). This indicates that extent of lesion alone cannot account for simultanagnosia.

The subtraction and overlap analyses suggest that simultanagnosia might be critically linked to white rather than grey matter damage. Therefore we tested whether simultanagnosia might be associated with relatively larger damage to white matter than grey matter. We computed a mixed ANOVA with the following factors: lesion volume (grey matter, white matter) and group (SM, neurological controls i.e. Bilat + LVS + RVS). We found a significant interaction of lesion volume (grey matter vs. white matter) and patient group (with vs. without simultanagnosia; $F(1,26)=4.21$, $p<0.05$). This interaction indicated that the volume of white matter lesions were significantly larger, compared to grey matter lesions, in the simultanagnosia patients ($t(6)=-2.90$, $p<0.05$) but not across the neurological control groups ($t(20)=-1.82$, $p>0.08$). Interestingly, the total volume of white matter lesions was not significantly larger in the simultanagnosia group (vs. the control patients, $t(26)=1.26$, $p>0.2$). Taken together, these results strongly indicate that simultanagnosia might be chiefly explained by white matter disconnection.

Lesion laterality. To investigate the role of bilateral lesions in simultanagnosia, we computed a lesion laterality index, where the closer to zero the higher the bilateral symmetry is. Not surprisingly the LVS and RVS groups showed clear asymmetrical grey and white matter lesions denoted by high laterality scores for all three brain regions (Figure 13A-C) and therefore they were not included in the follow up statistical analysis. In contrast the simultanagnosia patients (SM) showed a low laterality index mostly in parieto-occipital regions within white matter (Fig. 13C). Supporting this observation, a comparison between the SM patients and the Bilat group showed a significant lower laterality index for parieto-

occipital white matter lesions in the SM patients ($t(12)=-2.46$, $p<0.05$). No other reliable differences were found in the laterality pattern in any other brain regions. The laterality index analyses show that bilateral parieto-occipital white matter disconnections are both distinctive and necessary to create simultanagnosia.

Voxel-based morphometry. One caveat to the above analyses is that the patients' groups were pre-selected. This could introduce behavioural and anatomical biases and confounds by failing to rule out cases in the overall neuropsychological population where the damage may be found but the patients are symptomless. To overcome this as well as to control for the effects of potentially co-varying factors, such as age, time since lesion and lesion volume that could potentially affect cognitive performance, we supplemented the above analyses with a VBM approach applied in the context of a large unbiased sample of neuropsychological patients (see results in Tables 13-14 and Figures 14-15). VBM analyses of grey matter damage associated with simultanagnosia indicated lesions within frontal, parietal and occipital cortices. Specifically we found a link between simultanagnosia symptoms and grey matter damage within bilateral calcarine, cuneus and parieto-occipital fissure, left middle and superior occipital gyrus, bilateral middle frontal area (BA46 i.e. middle frontal and inferior frontal gyri) and superior frontal gurus, as well as right parietal areas including intraparietal sulcus, postcentral and superior parietal gyri and angular gyrus (Figure 14A; Table 13 Analysis 1). VBM analysis of the white matter damage associated with simultanagnosia indicated bilateral occipital and parieto-occipital lesions (suggesting damage within long association and commissural pathways including bilaterally the superior longitudinal, inferior fronto-occipital and inferior longitudinal fasciculi, corpus callosum, inferior longitudinal fasciculus, left corona corona radiata and left posterior thalamic radiation; Figure 15A; Table 14 Analysis 1).

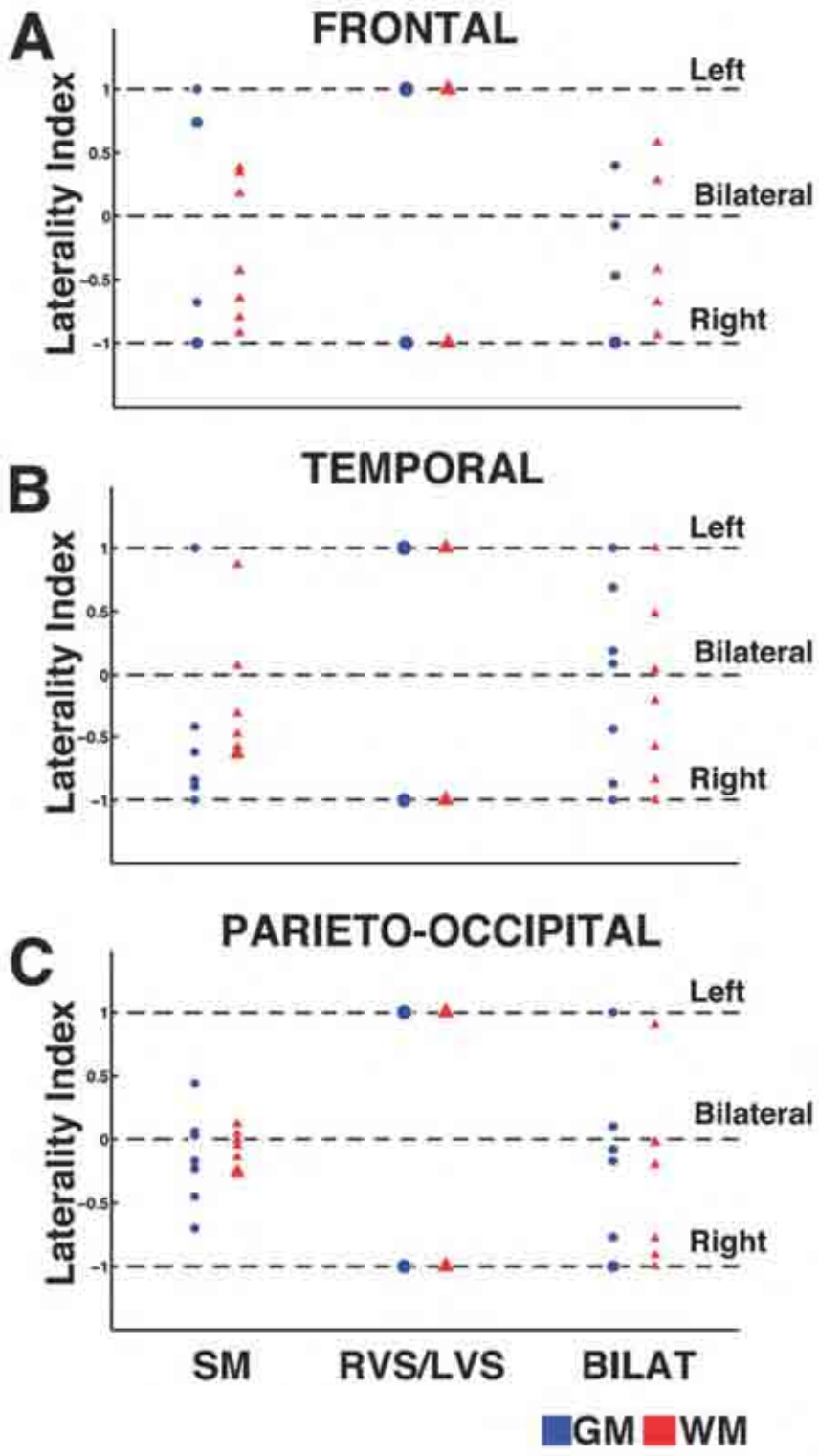

Figure 13. Lesion laterality indices within **(A)** frontal, **(B)** temporal and **(C)** parieto-occipital lobes estimated separately for the grey and white matter, plotted for patients in the simultanagnosic (SM) group and in three control groups (LVS, RVS and BILAT, see Methods for details). Blue circles indicate grey matter (GM) and red triangles indicate white matter (WM).

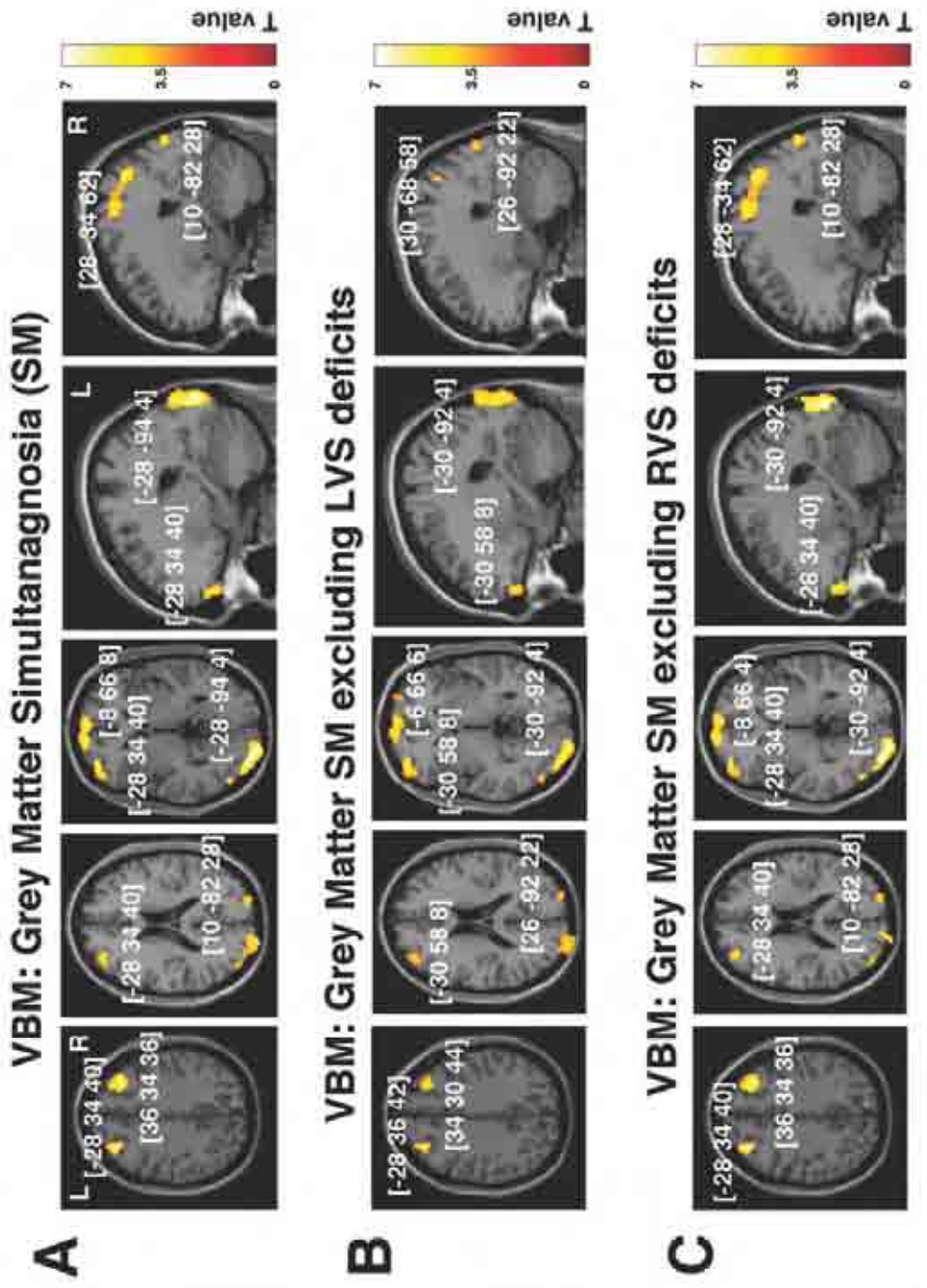

Figure 14. (A) Grey matter substrates of simultanagnosia (SM) - results from the VBM analysis designed to test the relationship between reduced grey matter volume (grey matter lesions) and simultanagnosia symptoms (*Analysis 1*). Grey matter substrates of simultanagnosia versus unilateral **(B)** left and **(C)** right visuospatial deficits. Dissociating simultanagnosia from either left visuospatial deficits (*Analysis 2*) or right visuospatial deficits (*Analysis 3*) was achieved by using exclusive masking. See Methods section for details of statistical models. SPM maps are overlaid on canonical T1 image. All images are displayed in neurological convention i.e. left of the slice represents the left hemisphere. Numbers in brackets indicate peak MNI coordinates.

Similarly to the lesion subtraction plots, in VBM analyses we used statistical models including additional covariate for left or right visuospatial deficits to dissociate simultanagnosia (SM) from unilateral symptoms such as neglect and visual extinction (LVS and RVS deficits). After controlling for unilateral deficits we found that grey matter lesions within bilateral calcarine, cuneus and parieto-occipital fissure, left middle and superior occipital gyrus, bilateral middle frontal area (BA46), bilateral superior frontal gurus and right intraparietal sulcus were exclusively associated with simultanagnosia (Figure 14B,C; Table 13 Analysis 2 and Analysis 3). These results also showed that, overall, simultanagnosia symptoms were not associated with damage to the inferior parietal lobule including the angular gyrus (i.e., areas typically associated with neglect; see Chechlacz et al., 2010; Hillis et al., 2005; Medina et al., 2009; Mort et al., 2003). Interestingly, we found that, while bilateral lesions within long association pathways including the superior longitudinal, inferior fronto-occipital and inferior longitudinal fasciculi result in simultanagnosia symptoms, unilateral disconnections within these pathways produce contralateral visuospatial deficits (Figure 15A,B; Table 14 Analysis 2 and Analysis 3). Similar results (albeit with weaker reliability) were obtained when we tested for the correlation between brain damage and simultanagnosia symptoms with the analyses based only on data from stroke patients (not shown).

DTI tractography. To further characterize the white matter lesions we next employed data and analyses procedures optimized for white matter based on diffusion tensor imaging. Information solely derived from the conventional T1 weighted MR images is not sufficient to accurately depict damage within specific white matter tracts. Therefore, to further examine white matter substrates of simultanagnosia, we examined the extent and laterality (left and right hemisphere changes in structural connectivity) of damage within a-priori tracts of interests: the superior longitudinal, inferior longitudinal and inferior fronto-occipital fasciculi.

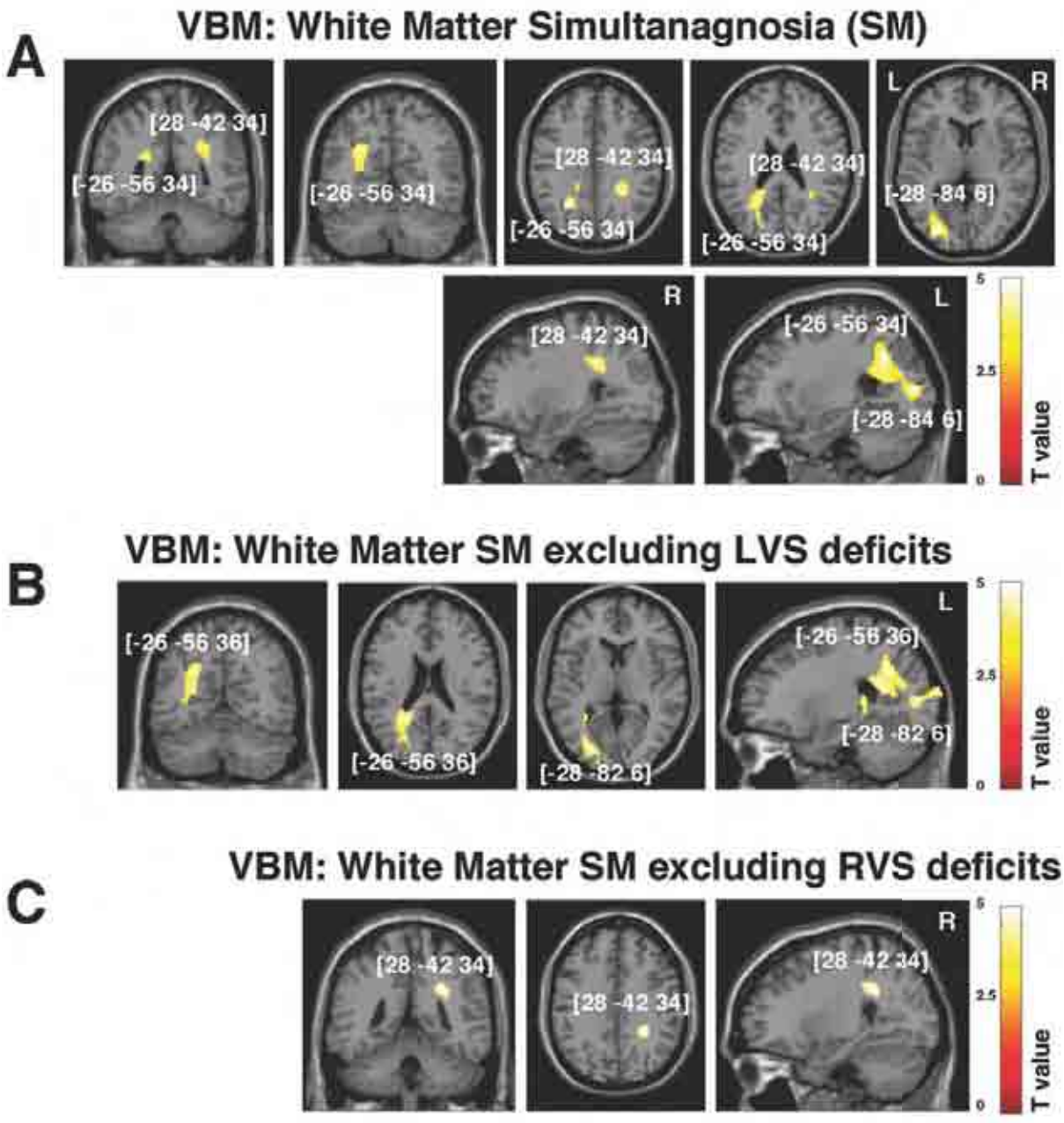

Figure 15. (A) White matter substrates of simultanagnosia (SM) - results from the VBM analysis designed to test the relationship between reduced white matter volume (white matter lesions) and simultanagnosia symptoms (*Analysis 1*). White matter substrates of simultanagnosia versus unilateral **(B)** left and **(C)** right visuospatial deficits. Dissociating simultanagnosia from either left visuospatial deficits (*Analysis 2*) or right visuospatial deficits (*Analysis 3*) was achieved by using exclusive masking. See Methods section for details of statistical models. SPM maps are overlaid on canonical T1 image. All images are displayed in neurological convention i.e. left of the slice represents the left hemisphere. Numbers in brackets indicate peak MNI coordinates.

We used streamline tractography and tract specific measures to directly evaluate damage within the three major tracts of interests: the SLF, ILF and IFOF. Tract reconstruction was computed for the 5 simultanagnosic patients and 20 age-matched healthy controls as well as for 5 LVS patients, 5 RVS patients and 7 chronic neurological patients without any visuospatial deficits. The results are presented in Figure 16. Within the healthy controls we observed large variability in the number of reconstructed streamlines for each fasciculus. This variability is expected when taking into account age differences across the control group (see for example Thomas et al., 2008). We nevertheless did not weight or correct the healthy control results by age or gender as this group was chosen to match the simultanagnosic patients and we wanted to avoid the need to apply any data transformations to the patients' data. Note that variability in the control data reduces the likelihood of finding reliable differences between the controls and the individual simultanagnosic patients.

We found that overall, the number of reconstructed streamlines across both hemispheres was significantly lower in simultanagnosic patients compared to healthy controls ($t(23)=-3.84$, $p<0.001$), which converges with the extensive white matter damage in the SM group, as demonstrated above by lesion analyses (Figure 16A). Tractography confirmed lesion overlap and VBM findings suggesting that lesions associated with simultanagnosia indeed affect bilaterally structural integrity of three long association pathways, SLF, IFOF and ILF (Figure 16B-D). We found a significant reduction in the number of streamlines in simultanagnosia patients compared to healthy controls within both left ($t(23)=-4.10$, $p<0.0005$) and right ($t(23)=-8.28$, $p<0.0001$) SLF, left ($t(23)=-3.0$, $p<0.01$) and right ($t(23)=-4.35$, $p<0.0005$) IFOF as well as left ($t(23)=-5.23$, $p<0.0001$) and right ($t(23)=-3.51$, $p<0.005$) ILF.

We next performed tracts reconstruction for three additional patients group: with left visuospatial deficits (LVS), right visuospatial deficits (RVS) and chronic neurological patients without any visuospatial deficits (CN). We used two-sample t-test, to compare the results of each patient group to the healthy controls. We note that due to the small number of patients in each group these results should be considered with cautions. The number of reconstructed streamlines for the CN group did not differ from that of the healthy controls (both across the whole brain and for individual white matter tracts). Not surprisingly, we found a significant reduction in the number of reconstructed streamlines in LVS patients compared to healthy controls within right SLF ($t(23)=-5.57$, $p<0.0001$) and right IFOF ($t(23)=-3.75$, $p<0.001$). We also found a significant reduction in the number of reconstructed streamlines in RVS patients compared to healthy controls within left IFOF ($t(23)=-3.59$, $p<0.005$). These results are consistent with previous reports indicating unilateral damage within these white matter pathways in patients with contralateral visuospatial deficits (e.g. Chechlacz et al., 2010; He et al., 2007; Thiebaut de Schotten et al., 2008; Urbanski et al., 2008). There was no significant difference in the number of reconstructed streamlines within these damaged white matter tracts between the simultanagnosia patients and patients with unilateral visuospatial deficits (right SLF: SM vs. LVS, $t(8)=0.05$, $p>0.5$; right IFOF: SM vs. LVS, $t(8)=-0.47$, $p>0.5$; left IFOF: SM vs. RVS, $t(8)=1.02$, $p>0.1$). Thus the magnitude of any white matter tract disconnection within one hemisphere was not critical for simultanagnosia symptoms, but the presence of bilateral damage to fibre pathways was. Taken together, the tractography analyses revealed that visuospatial attention deficits in simultanagnosic patients were associated with bilateral lesions (significant reduction in structural connectivity) within all three examined long association pathways, the SLF, IFOF and ILF interconnecting fronto-parieto-occipital regions.

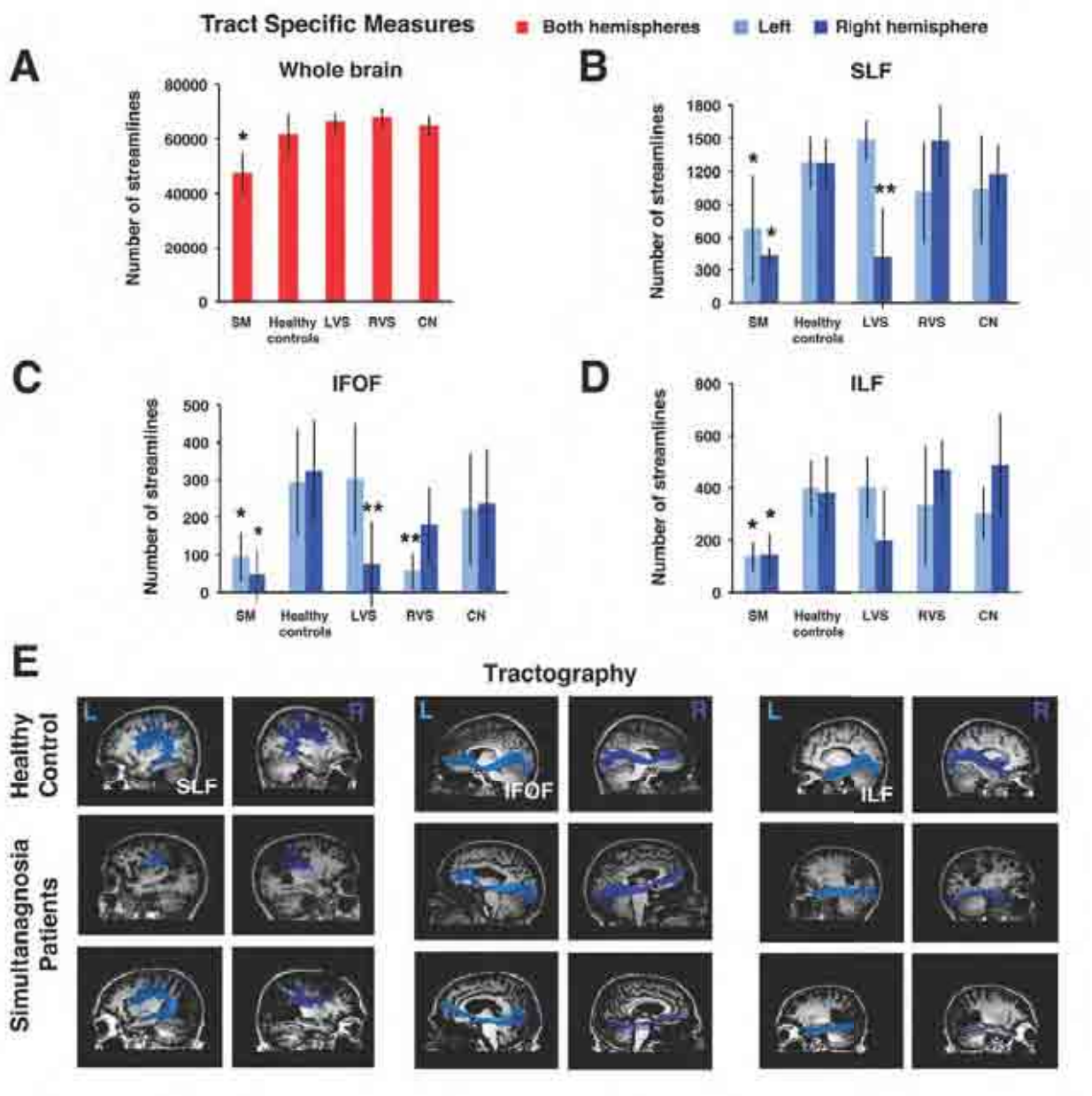

Figure 16. The number of reconstructed streamlines for **(A)** the whole brain and **(B-D)** the three fasciculi (SLF, IFOF and ILF; left and right hemisphere separately) in simultanagnosic (SM) patients (n=5), patients with left visuospatial deficits and right brain lesions (LVS, n=5), patients with right visuospatial deficits and left brain lesions (RVS, n=5), chronic neurological patients without any visuospatial deficits with either bilateral or left or right brain lesions (CN, n=7) and age matched healthy controls (n=20). In **(A-D)** the error bars indicate the standard deviation; * indicates fasciculi with significantly reduced structural integrity in simultanagnosic patients and ** indicates fasciculi with significantly reduced structural integrity in control patient groups (LVS, RVS, CN) i.e. the number of streamlines was significantly reduced compared to controls ($p<0.01$; see Results for details). **(E)** Examples of reconstructed IFOF, ILF and SLF for one of the healthy controls and two of the simultanagnosic patients. The tracts are displayed on a corresponding T1 scan in parasagittal view. L, left hemisphere (light blue), R, right hemisphere (dark blue), Whole brain i.e. both

hemispheres (red); CN = chronic neurological; LVS = left visuospatial deficits; RVS= right visuospatial deficits; SM= simultanagnosia; IFOF = inferior fronto-occipital fasciculus, ILF = inferior longitudinal fasciculus, SLF = superior longitudinal fasciculus.

DISCUSSION

To date the understanding of simultanagnosia has been limited largely to case studies, making it difficult to assess the underlying neuronal substrates. Although bilateral parieto-occipital and posterior parietal (including angular gyrus) lesions have been reported, these also occur in combination with damage within other brain regions including frontal cortex and pulvinar (Bálint, 1909; Holmes, 1918; Coslett and Saffran, 1991; Hausser et al., 1980; Humphreys et al., 2000; Jackson et al., 2004; Ogren et al., 1984; Rizzo and Vecera, 2002). In the current study we evaluated the contrasting grey and white matter substrates of i) simultanagnosia (SM) vs. co-occurring visuospatial deficits (neglect/extinction), ii) simultanagnosia vs. bilateral control patients without visuospatial deficits, and (iii) an unbiased sample of neurological patients to decompose the neuroanatomical substrates of the syndrome and to gain insights into structural and functional organization of visuospatial attention networks. The bilateral disconnection account of simultanagnosia was also examined using DTI imaging. Importantly, despite using various lesion symptom-mapping approaches, the results converge to provide strong and reliable evidence for the neural substrates of simultanagnosia.

Simultanagnosia as a disconnection syndrome

The results indicated that, along with any associated cortical damage, the symptoms associated with simultanagnosia are linked to extensive disconnection within white matter pathways subserving visual processing and spatial attention. As noted in the Introduction, simultanagnosic deficits have been attributed to severe impairments in visual processing speed (Duncan et al., 1999; Duncan et al., 2003) in accordance with the Theory of Visual

Attention (TVA; Bundesen, 1990). Our findings fit with this idea in the sense that deficits in processing speed might follow from extensive bilateral white matter disconnections. Further analyses revealed that bilateral parieto-occipital white matter disconnections within the syndrome are both distinctive (see below for discussion in relation to neglect and organization of visuosptatial attention network) and necessary to create symptoms associated with simultanagnosia.

We used tractography to provide direct evidence of disconnection within major parieto-occipital and fronto-occipital networks in simultanangnosia. We examined structural integrity within three long association tracts: the SLF connecting frontal, parietal and temporal cortices, the ILF connecting temporal and occipital cortices, and the IFOF connecting frontal and occipital cortices. We found that simultanagnosia is associated with damage within all three long association pathways. It has been proposed that cognitive deficits in simultanagnosia affect different aspects of spatial attention, including the consolidation of information into visual working memory and thus the link between damage to either left or right ILF and impaired visual recent memory (Tusa and Ungerleider, 1985) might provide one of the keys to understanding at least some simultanagnosia symptoms. Previous studies point to SLF as one of the main components of the frontoparietal attention network (Makris et al., 2005; Mesulam, 1981; Petrides and Pandya, 2006; Schmahmann and Pandya, 2006) and disruptive connectivity within right SLF has been reported in connection with behavioural deficits in the neglect syndrome (Bartolomeo et al., 2007; Chechlacz et al., 2010; Karnath et al., 2009; Thiebaut de Schotten et al., 2008; Thiebaut de Schotten et al., 2005). The IFOF links the occipital and frontal lobes and passes under parietal cortex. Previous work has suggested that the direct fronto-parietal connection is critical for attention, spatial and visual processing (Aralasmak et al., 2006; Doricchi et al., 2008; Fox et al., 2008).

Additionally, it has been proposed that right or bilateral damage within the IFOF, in conjunction with damage to posterior parietal cortex, could result in impaired simultaneous perception as well as causing optic ataxia and oculomotor apraxia (Aralasmak et al., 2006; Battelli et al., 2003; Ghika et al., 1998; Stasheff and Barton, 2001). Interestingly, some of our simultanagnosia patients also suffered from other symptoms of full Balint's syndrome i.e. optic ataxia and oculomotor apraxia (not reported here) and taking into account individual differences in the lesion pattern and severity of symptoms, further work is needed to link the severity of Bálint's symptoms to the extent of loss of structural integrity within IFOF and other long association pathways. Nevertheless we propose here that bilateral damage to the parieto-occipital cortex and the right intraparietal sulcus, together with underlying bilateral white matter lesions, contributes to poor visual processing of multiple objects and the loss of processing speed in simultanagnosia, whereas additional fronto-parieto-occipital disconnections might results in increased severity of symptoms and further visuosptatial problems.

Visuospatial attention network: simultanagnosia and other neuropsychological syndromes

The current study provides strong evidence that although the areas of damage in patients with simultanagnosia, extinction and neglect can partially overlap, the cortical substrates of simultanagnosia symptoms are separate from those characterising the other syndromes. In particular, simultanagnosia is associated with damage to the middle frontal area (BA46), parieto-occipital and middle occipital regions, while neglect is typically associated with lesions including the temporal parietal junction, superior temporal gyrus and angular gyrus (Chechlacz et al., 2010 [Chapter2]; Hillis et al., 2005; Karnath et al., 2004; Mort et al., 2003; Vallar, 2001; Vallar et al., 2003). This contradicts the argument that simultanagnosia/Bálint's syndrome constitutes a form of double neglect, at least in terms of cortical damage (Farah,

1990). However, could there be a form of double neglect generated through sub-cortical disconnection? Damage within right SLF, IFOF and ILF has been reported in neglect patients (ILF, Bird et al., 2006); SLF, Chechlacz et al., 2010 [see Chapter 2]; He et al., 2007; Thiebaut de Schotten et al., 2008); IFOF, Chechlacz et al., 2010; Urbanski et al., 2008) and bilateral damage within these tracts is found in simultanangnosia. One account of these data is that the white matter damage common to the disorders reflects a slowed rate of information processing (cf. Duncan et al., 1999; Duncan et al., 2003), and this may exacerbate the spatial biases leading to neglect and extinction (see Robertson and Manly, 1999). This would be less a form of 'double neglect' than an additional contributing factor that is nevertheless functionally distinct from the spatial bias that is key to neglect and extinction. In simultanagnosia, the pronounced white matter damage leads to the slowed processing being the dominant factor and to generally poor awareness of multiple stimuli.

Although, the double neglect account of simultanagnosia is not plausible, undoubtedly the current study provides evidence that both simultanangnosia and unilateral visuospatial attention deficits result from disconnection within a common neuronal network (see Figure 15 and 16). While distinct cortical regions seem to control shifts of attention, visual selection, target detection and so on, common white matter pathways support interactions across these different cortical regions. The organization of neuronal network for visuospatial attention has been recently examined by a study using probabilistic tractography approach to investigate structural connectivity between neuronal substrates of attention identified based on functional imaging (Umarova et al., 2010). The study proposed a visuospatial attention network consisting of both dorsal (connecting temporoparietal with frontal regions) and ventral (travelling from temporoparietal regions towards pars triangularis of the inferior frontal gyrus, insula and putamen) pathways. The dorsal pathways identified by Umarova et al. (2010) have

been assigned to the SLF (most likely to two of its subcomponents, SLFII and SLFIII) and the ventral pathway to either anterior IFOF or ILF and the external capsule fibre system. Due to the nature of the paradigm used, the above study (Umarova et al., 2010) only described the components of the visuospatial attention network within the right hemisphere. The results of the current study indicate that a bilaterally organized visuospatial attention network underlies different aspects of visual selection and spatial attention.

Dorsal and Ventral Simultanagnosia

One final point to be raised is the relation between so-called 'dorsal' and 'ventral' simultanagnosia, as labelled by Farah (1990). Historically the term simultanagnosia refers to patients with poor ability to interpret complex visual displays but in fact it has been often applied in the context of two somewhat different deficits and two different groups of patients (Farah, 1990). Specifically, the term dorsal simultanangnosia has been used to classify poor interpretation of scenes resulting from impaired spatial awareness of more than one object at time and has been mainly linked to bilateral parieto-occipital lesions (Farah, 1990; Luria, 1959). In contrast, ventral simultanagnosia has been noted after unilateral damage to the left posterior venral cortex mainly involving temporo-occipital regions (see Kinsbourne and Warrington, 1962) and is characterised by symptoms such as alexia and impaired reporting of multiple letters under brief exposure conditions. On one hand, such patients do not show poor interpretation of scenes per se, but their letter-by-letter reading is accompanied by impairment in describing complex pictures despite ability to see more than one object at time (Humphreys and Price, 1994; Kinsbourne and Warrington, 1962).

In the current study patients were classified as having simultanagnosia based on dual-symptom definition (poor scene interpretation plus multiple letter report). Our neuroimaging analyses indicated an association between bilateral parieto-occipital disconnections and the

dual symptom characterisation of simultanagnosia representing a deficit that is neither material-specific nor linked to a process such as naming (most of our simultanagnosia group had no naming problems). Interestingly, our VBM analysis of grey matter also indicated a link between the symptoms of simultanagnosia and left occipital lesions (i.e. the lesion pattern characteristic for ventral simultanagnosia). This could be partially attributed to the dual symptom characterization of simultanagnosia, but it could also point to functional similarities between dorsal and ventral simultanangnosia. Although Coslett and Safran (Coslett and Saffran, 1991) suggested that dorsal and ventral simultanagnosia result from completely different impairments, Duncan et al.'s (2003) findings indicate a common functional deficit, as they showed that both types of patient suffered from severe impairments in processing speed. We conclude that simultanagnosia does represent a general problem such as slowed visual processing that impacts on all tasks requiring the rapid assimilation of visual information across the field.

Methodological Consideration

Simultanagnosia is often reported in patients with different aetiologies, including corticobasal degeneration (CBD) and posterior cortical atrophy (e.g. Mendez, 2000; Mendez and Cherrier, 1998). We opted to base our study on a non pre-selected clinical cohort with different clinical aetiologies (mainly stroke, but also CBD and encephalitis; see Table 11 and 12) as two of the simultanagnosic patients (out of seven included in the study) suffered from CBD. Furthermore, pooling across different neurological aetiologies and using VBM facilitates understanding of brain behaviour relationships by generalizing the inferences across different causes of brain lesion. Importantly, VBM is sensitive to tissue changes outside the main lesion, including white and grey matter atrophy, and this is important as we studied patients in the chronic stage of the disorder. The atrophy may be a factor contributing

to the functional deficit at this stage (see Gottesman et al., 2008 for evidence in relation to unilateral visuospatial deficits). However, our approach has limitations. These are mainly due to the fact that the neuroimaging data (anatomical scans only) used here are susceptible to shortcomings in terms of capturing all brain changes contributing to cognitive deficits (e.g. tissue malperfusion). Thus it is possible that we provided here an underestimation of the contribution the relevant brain areas related to simultanagnosia. Further work is required to test this possibility.

Conclusions

We conclude that our findings provide evidence that lesions associated with simultanangnosia are different than those associated with unilateral spatial attention syndromes such as neglect and extinction. The critical lesions associated with simultanagnosia occupy the parieto-occipital and middle occipital regions as well as the middle frontal area (BA46), while lesions within the temporal parietal junction and inferior parietal lobule (angular gyrus) are associated with unilateral symptoms. Furthermore, not only the different pattern of grey matter lesions but also the bilaterality of white matter disconnections in individual neuropsychological patients determine the degree to which visual processing and spatial attention are disrupted and thus the nature of visuospatial deficits. We note, that the analysis approach used here specifically tested for lesions that were associated with simultanagnosia while controlling for other spatial attention deficits. Therefore, this study highlights the differences rather than the commonalities across the various spatial attention deficits.

Table 13. Grey matter substrates of simultanagnosia.

Contrast	Cluster level		Voxel level	Coordinates			Brain Structure
	P_{FWE}	Size	Z-score	X	Y	Z	
Simultanagnosia							
VBM: Analysis 1	0.000	1687	5.79	**-28**	**-94**	**4**	Left MOG and SOG, calcarine, cuneus, parieto-occip fissure
	0.000	2085	5.36	**-28**	**34**	**40**	Left MFG and IFG, bilateral SFG
			5.32	-8	66	8	
			5.12	8	64	0	
	0.000	551	5.26	**36**	**34**	**36**	Right IFG and MFG
	0.000	1049	4.89	**28**	**-34**	**62**	Right postcentral and superior parietal gyri,
			4.87	24	-60	56	intraparietal sulcus and angular gyrus
	0.000	400	4.72	**10**	**-82**	**28**	Right calcarine, parieto-occip fissure, cuneus
Simultanagnosia excluding LVS deficits							
VBM: Analysis 2	0.000	435	6.10	**-28**	**36**	**42**	Left MFG and IFG
	0.000	1137	5.58	**-30**	**58**	**8**	Left MFG and SFG
	0.000	1332	5.37	**-30**	**-92**	**4**	Left MOG, SOG, calcarine, cuneus, parieto-occip fissure
	0.000	598	5.19	**-6**	**66**	**6**	Bilateral SFG
			4.90	8	64	0	
	0.000	505	4.75	**34**	**30**	**44**	Right IFG and MFG

	0.000	255	4.25	**26**	**-92**	**22**	Right calcarine, parieto-occip fissure, cuneus
	0.000	121	3.94	**30**	**-68**	**58**	Right intraparietal sulcus
Simultanagnosia excluding RVS deficits							
VBM analysis 3	0.000	1468	5.77	**-30**	**-92**	**4**	Left MOG and SOG, calcarine, cuneus, parieto-occip fissure
	0.000	1840	5.35	**-28**	**34**	**40**	Left MFG and IFG, bilateral SFG
			5.18	-8	66	4	
			5.13	8	64	0	
	0.000	371	5.22	**36**	**34**	**36**	Right IFG and MFG
	0.000	1018	4.80	**28**	**-34**	**62**	Right postcentral and superior parietal gyri,
			4.79	24	-60	56	intraparietal sulcus and angular gyrus
	0.000	403	4.73	**10**	**-82**	**28**	Right calcarine, parieto-occip fissure, cuneus

IFG, inferior frontal gyrus; MFG, middle frontal gyrus; MOG, middle occipital gyrus; SFG, superior frontal gyrus; SOG, superior occipital gyrus;

Table 14. White matter substrates of simultanagnosia.

Contrast	Cluster level		Voxel level	Coordinates			Brain Structure
	P_{FWE}	Size	Z-score	X	Y	Z	
Simultanagnosia							
VBM: Analysis 1	0.000	1783	4.16	**-28**	**-84**	**6**	Left IFOF, ILF, post. TR Left SLF, post. CR,
			4.04	-26	-56	34	IFOF, corpus callosum, post. TR
	0.000	243	3.83	**28**	**-42**	**34**	Right SLF, IFOF, ILF
Simultanagnosia excluding LVS deficits							
VBM: Analysis 2	0.000	2109	4.35	**-28**	**-82**	**6**	Left IFOF, ILF, post. TR
			4.27	-18	-100	14	Left IFOF, post. CR
			4.13	-26	-56	36	Left SLF, post. CR, IFOF, corpus callosum, post. TR
Simultanagnosia excluding RVS deficits							
VBM analysis 3	0.000	167	4.02	**28**	**-42**	**34**	Right SLF, IFOF, ILF

CR, corona radiata; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; post. posterior; SLF, superior longitudinal fasciculus; TR, thalamic radiation;

CHAPTER 5:

ACUTE VS. CHRONIC PROGNOSIS OF ALLOCENTRIC AND EGOCENTRIC NEGLECT SYMPTOMS BASED ON CLINICAL SCANS[14]

[14] This Chapter has been submitted to *Cortex (under review)*

ABSTRACT

The study contrasted the neuroanatomical substrates of acute and chronic visuospatial deficits associated with different aspects of unilateral neglect using computed tomography scans acquired as part of routine clinical diagnosis. We employed voxel-wise statistical analyses on a group of 160 stroke patients scanned at a sub-acute stage and lesion-deficit relationships were assessed across the whole brain, separately for grey and white matter, relative to behavioural data collected within 3 months and after 9 months post lesion. We found that lesions in the angular gyrus were associated with persistent allocentric neglect. In contrast, lesions within the superior temporal gyrus extending into the supramarginal gyrus, as well as lesions within the basal ganglia and insula, were associated with persistent egocentric neglect. Damage within the temporo-parietal junction was associated with both types of neglect at 9 months. Finally, we demonstrated that white matter disconnections resulting from damage along the superior longitudinal fasciculus were associated with both types of neglect symptoms and critically related to both subacute and chronic deficits. We discuss the implications for understanding the neglect syndrome, for recovery of function and for using clinical scans to predict outcome.

INTRODUCTION

Persistent visuospatial deficits are often associated with overall poor functional outcome following stroke (Buxbaum et al., 2004; Cherney et al., 2001). The most common visuospatial disorder associated with stroke is unilateral neglect (Stone et al., 1993). While neglect symptoms recover rapidly in some patients, in other cases the problems persist and contribute significantly to poor return to independent living (Campbell and Oxbury, 1976;

Denes et al., 1982; Luaute et al., 2006). It is thus important to delineate which lesions are associated with persistent neglect symptoms and which with recovery of function.

Different forms of neglect

Unilateral neglect is diagnosed when patients fail to attend to stimuli presented on the side of space contralateral to their lesions (Heilman and Valenstein, 1979). However, unilateral neglect represents a complex syndrome with different patients showing a varied combination of impairments (Buxbaum et al., 2004; Kerkhoff, 2001). Dissociable cognitive deficits within the neglect syndrome have now been reported both across a variety of different measures (e.g., line cancellation vs. bisection) and even within the same task (Bickerton et al., 2011; Buxbaum et al., 2004; Verdon et al., 2010). Dissociations can be found between the presence of neglect symptoms in different modalities as well as between different sectors of space (Committeri et al., 2007; Halligan and Marshall, 1991; Hillis et al., 2005; Kerkhoff, 2001; Marsh and Hillis, 2008; Vuilleumier et al., 1998). Of most relevance to the current study is the dissociation between egocentric neglect, expressed through inattention to stimuli presented on the contralesional side of the body (Doricchi and Galati, 2000; Riddoch and Humphreys, 1983), and allocentric neglect, shown by poor report of elements on the contralesional side of individual objects (Doricchi and Galati, 2000; Kleinman et al., 2007; Olson, 2003; Walker et al., 1996; Walker and Young, 1996). It is striking that egocentric and allocentric can be found on different sides of space even in the same individual (e.g., Humphreys and Riddoch, 1994a, 1995), following bilateral lesions. This contrasting pattern of spatial deficit within single cases makes it difficult to account for the dissociation in terms of a single gradient of deficit across space (cf. Driver and Pouget, 2000). Rather the data fit with the notion that different visual representations are coded within the brain perhaps for

different purposes (e.g., egocentric representations to help guide spatial exploration; allocentric representation for object recognition; see Heinke and Humphreys, 2003, for one explicit computational account).

The neuroanatomy of neglect

There is also evidence that egocentric and allocentric neglect are associated with different brain lesions (Hillis et al., 2005; Medina et al., 2009; Chechlacz et al., 2010 [Chapter 2 here]; Verdon et al., 2010; see below).

For example, Chechlacz et al (2010) demonstrated that, after right hemisphere damage, allocentric neglect is associated with lesions to the posterior superior temporal sulcus, angular, middle temporal/inferior temporal and middle occipital gyri, while egocentric neglect was linked to more anterior lesions including the middle frontal, postcentral, supramarginal and superior temporal gyri and the insula. In contrast, damage to the right temporo-parietal junction was associated with both forms of neglect. Similar dissociations have been noted by several other groups (e.g., Hillis et al., 2005; Medina et al., 2009; Verdon et al., 2010). These contrasting lesion sites, linked to different neglect symptoms, may help to explain previous disparities in lesion-symptom mapping in the syndrome (on the one hand see Vallar et al., 2003; Vallar and Perani, 1986; Mort et al., 2003; on the other see Karnath, 2001; Karnath et al., 2001; Ticini et al., 2010).

In addition to the grey matter lesions associated with neglect there are also white matter lesions, which disrupt connectivity within attentional networks and this has led some researchers to regard neglect as a disconnection syndrome (Bartolomeo et al., 2007; Doricchi and Tomaiuolo, 2003). Specifically, neglect has been reported following damage to the superior longitudinal (SLF; Chechlacz et al., 2010 [see Chapter 2]; He et al., 2007; Thiebaut

de Schotten et al., 2008), the inferior longitudinal (ILF; Bird et al., 2006, Chechlacz et al., 2010; Riddoch et al., 2010) and the inferior fronto-occipital fasciculi (IFOF; Chechlacz et al., 2010; Riddoch et al., 2010; Urbanski et al., 2008). Interestingly, Chechlacz et al (2010) found that damage within long association pathways including the ILF, the IFOF and the SLF, were linked to both allocentric and egocentric neglect. They suggested that the different representations of space, formed in different cortical regions, were linked to anterior, action control areas of the brain through common white matter tracts.

Recovery of function

The recovery rates from unilateral neglect following stroke vary between reports but roughly about one third of patients show persistent visuospatial problems several months after stroke (Campbell and Oxbury, 1976; Cherney et al., 2001; Denes et al., 1982). It has been postulated that several different factors might have a significant impact on neglect recovery including the initial severity of the deficit(s), the presence of visual field defects, age and age-associated brain atrophy as well as lesion size and location (Campbell and Oxbury, 1976; Cassidy et al., 1999; Cherney and Halper, 2001; Farne et al., 2004; Gottesman et al., 2008; Levine et al., 1986; Samuelsson et al., 1997; Stone et al., 1992; Kertesz and Dobrowolski, 1981). Several studies indicate that neglect recovery can be predicted from neuroanatomical data (Farne et al., 2004; Karnath et al., 2011; Maguire and Ogden, 2002; Samuelsson et al., 1997). For example Maguire and Ogden (2002) have shown that persistent neglect is associated with lesions that involve at least three cortical lobes as well as the basal ganglia but that parietal lesions per se are not essential for chronic neglect. Karnath et al. (2011) provide additional evidence that lesions within the temporal cortex (including the superior and middle temporal gyri) and basal ganglia play a critical role for predicting chronic neglect. Recovery

can also be linked to white matter damage. Samuelsson et al (1997) reported that chronic neglect was highly correlated with damage of paraventricular white matter within the temporal lobe while Karnath et al. (2011) linked damage to the inferior fronto-occipital (IFOF) and uncinate fasciculi to chronic as well as acute neglect.

While these studies clearly suggest significant relationships between the location of brain damage and post-stroke neglect recovery, none of these reports takes into account the heterogeneity of neglect deficits in relation to the presence of a spatial disorder in chronic cases. One step towards this was recently reported by Kurshid et al. (2011) who noted that reperfusion of contrasting cortical areas can also predict recovery of different neglect symptoms in the acute stage after stroke – for example, they found that reperfusion of ventro occipito-temporal regions 3-5 days post lesion was linked to improvements in allocentric neglect while reperfusion of more dorsal fronto-parietal areas was associated with improvements in egocentric neglect. Furthermore, only one of these previous reports (Karnath et al., 2011) has employed modern voxel-wise analysis of neuroimaging data, while others are based on simple group comparisons and lesion overlap methods. These methods can be susceptible to assigning impairment to brain regions, which happen to have increased vulnerability to damage rather than being involved in particular cognitive functions. In addition, the studies have tended to use binary classification of patients (with and without 'neglect') and analyses based on predefined brain regions, and so may fail to detect either sub-divisions within regions or lesion-symptom relations outside of the defined areas. Here we assessed the neuroanatomical correlates of acute vs. persistent visuospatial deficits associated with two distinct aspects of the neglect syndrome – egocentric and allocentric neglect (cf. Chechlacz et al., 2010 [Chapter 2 here]; Marsh and Hillis, 2008; Medina et al., 2009; Verdon et al., 2010). Interestingly, in an analysis of a large-scale screen of stroke

patients using the Apples test that we employ, Bickerton et al. (2011) noted that impairments in allocentric neglect are predictive of poor functional outcome in patients (e.g., on the Barthel index), while this is not necessarily the case for egocentric neglect. In addition the two forms of neglect correlated with different behavioural impairments (allocentric neglect with aspects of gesture reproduction, egocentric neglect with performance on multi-step tasks), highlighting the need to distinguish the different spatial impairments when attempting to predict outcome from lesion data. Our analyses also controlled for potential confounding factors such as aetiology (the type of stroke: ischemia or hemorrhage), age-related changes, time from stroke to scan and as well as patient overall orientation and anosagnosia. This enabled us to examine the neuronal substrates of neglect symptoms at acute vs. chronic stages, with effects of other factors, which may co-vary with recovery, eliminated. In addition to this, we go beyond prior work by using clinical scans derived as part of the routine clinical care for patients. We employed whole brain statistical analyses (voxel-based morphometry VBM; Ashburner and Friston, 2000) to evaluate common structure-function relationships across the whole brain, separately for grey and white matter. The analysis was performed on CT scans and treated the behavioural measurements as continuous variables rather than as categorical scores, which increased both the ability to tease apart the different types of neglect and the sensitivity for detecting brain-behaviour associations. The severity of neglect symptoms was assessed based on a single task (the Apples test) that simultaneously distinguishes allocentric and egocentric neglect. This allowed us to control for variability in performance due to differential task demands, test conditions and stimuli that could potentially arise when using measures of the two types of neglect in different tasks.

Table 15. Patients' details: clinical and demographic data

	Neglect* (n=53)		**No neglect (n=107)**	
	Acute/Subacute	Chronic	Acute/Subacute	Chronic
Age in years (mean/SD)	69.3/12.3	N/A	68.3/12.7	N/A
Sex (M/F)	28/25	N/A	64/43	N/A
Aetiology (ISCH/BL)	45/8	N/A	99/8	N/A
Handedness (L/R)	47/6	N/A	94/13	N/A
Scan time since stroke in days (mean/SD)	5.5/12.9	N/A	3.2/7.7	N/A
BUCS** in days (mean/SD)	28.5/21.5	280.3/14.1	21.3/17.3	282.1/16.3
Orient1 mean/SD (max/range)	7.5/1.3 (8/1-8)	7.8/0.6 (8/7-8)	7.6/1.2 (8/3-8)	7.8/0.9 (8/5-8)
Orient2 mean/SD (max/range)	5.4/1.0 (6/2-6)	5.6/0.9 (6/1-6)	5.7/0.7 (6/3-6)	5.9/0.3 (6/4-6)
Nosognosia (Orient3) mean/SD (max/range)	2.8/0.5 (3/0-3)	3.0/0.2 (3/2-3)	2.9/0.3 (3/1-3)	3.0/0.2 (3/2-3)
Left VE (uni asymmetry) mean/SD (max/range)	0.5/1.2 (4/0-4)	0.2/0.8(4/0-4)	0.1/0.4 (4/0-4)	0/0 (4/0)
Right VE (uni asymmetry) mean/SD (max/range)	0.4/1.1 (4/0-4)	0.3/1.0/ (4/0-4)	0.1/0.7 (4/0-4)	0.1/0.7 (4/0-4)
Left VE (bilat asymmetry) mean/SD (max/range)	2.0/3.0 (8/0-8)	1.1/2.3 (8/0-8)	0.1/0.8 (8/0-8)	0.1/0.2 (8/0-1)

Right VE (bilat asymmetry) mean/SD (max/range)	0.7/2.2 (8/0-8)	0.6/2.1 (8/0-8)	0.3/1.4 (8/0-8)	0.2/1.0 (8/0-8)
ACT accuracy mean/SD (max/range)	28.4/14.7 (50/1-49)	38.2/11.1 (50/15-49)	47.4/4.4 (50/35-50)	46.9/4.0 (50/31-50)
ACT/AFA (left deficits) mean/SD (max/range)	4.8/6.0 (25/0-20)	2.8/4.4 (25/0-20)	0.4/0.7 (25/0-3)	0.5/1.0 (25/0-4)
ACT/AFA (right deficits) mean/SD (max/range)	1.0/2.2 (25/0-10)	1.3/3.2(25/0-14)	0.4/0.8 (25/0-4)	0.4/0.8 (25/0-2)
ACT/AIncA (left deficits) mean/SD (max/range)	3.1/5.1 (50/0-19)	1.3/3.0 (50/0-17)	0.1/0.2 (50/0-1)	0.1/0.4 (50/0-2)
ACT/AIncA (right deficits) mean/SD (max/range)	1.0/2.0 (50/0-11)	0.5/1.8 (50/0-6)	0.1/0.3 (50/0-1)	0.2/0.6(50/0-3)

*patient who at acute/subacute phase following stroke showed any type of neglect symptoms including egocentric and allocentric neglect for either left or right side of space; **For the acute/subacute phase the number of days indicate stroke to test (initial BUCS) interval and at the chronic phase number of days indicate the interval between initial BUCS test and follow up BUCS;
ACT, Apple Cancellation task; the maximum achievable score in the Apple Cancellation task is 50 (ACT accuracy). The cut-off for total numbers of target (full apples) omissions i.e. accuracy score is 40/50. Egocentric neglect is determined by whether patients miss targets (complete apples) on the left or right side of the page (asymmetry score calculated based on left- vs. right-side errors, ACT/AFA asymmetry score for full apples indicating either left or right deficits). Allocentric neglect is determined by whether patients make false positive responses by cancelling incomplete apples (distractors) where the gap is on either the right or left side of each apple, irrespective of the position of the (incomplete) apple on the page (asymmetry score calculated based on left- vs. right-side errors, AIncA asymmetry score for incomplete apples); BL, bleed/ hemorrhagic stroke; F, female; ISCH, ischemic stroke L, left; M, male; max/range, maximum achievable score and range of scores within the group of patients; Orient1, orientation measure assessing personal information; Orient2, orientation measure assessing time and space awareness; R, right; SD; standard deviation; VE, visual extinction test, the task consists of 4 unilateral left, 4 unilateral right and 8 bilateral trials, asymmetry score calculated based on left- vs. right-side misses;

METHODS

Participants

A total of 160 sub-acute stroke patients (92 males and 68 females; average age of 68.7 years, range 31 to 91 years; see Table 15 for full demographic and clinical data) were included. All patients were recruited as part of the BUCS project (Birmingham University Cognitive Screen, http://www.bucs.bham.ac.uk) from participating stroke units across the West Midlands area (United Kingdom). The analysis was performed both on patients who suffered ischemic stroke (144 patients) and hemorrhagic stroke (16 patients). All patients were in the sub-acute phase (<3 months) following stroke when their cognitive profile (behavioural data) was first assessed (based on BUCS, see below), with the average of stroke to testing interval of 24 days. All 160 patients were also examined at the chronic stage following stroke, approximately 9 months after initial behavioural testing. Behavioural data were only collected from patients who were physically stable, willing to perform the task and had a concentration span of at least ~60 minutes (judged clinically). We excluded from the study patients with enlarged ventricles and with poor quality of CT scans in order to prevent artifacts in the neuroimaging analyses. Clinical and demographic data were obtained from the patients' clinical files. All participants provided written informed consent in agreement with ethics protocols approved by the National NHS ethic committee and local NHS trusts.

Behavioural measures

Cognitive profile. The initial neuropsychological testing took place in the sub-acute phase following stroke onset and the average stroke to test interval was 24 days (±19.5; with 95% of patients being tested within two months and 78% of patients being tested within 1 month). The follow up neuropsychological testing was carried out at the chronic phase approximately 9 months following initial testing with the average test to test interval of 281

days (±15.6). The cognitive profile of each patient was derived using the BCoS, a test instrument developed to screen patients for a range of cognitive problems following stroke onset (Humphreys et al., 2011). The BCoS is aphasia and neglect-friendly and within 1 hour provides assessment based on 23 tests within 5 broad cognitive domains: Attention and Executive functions, Memory, Language, Praxis/Control and planning of action, and Mathematical/Number abilities. For the sub-acute tests, the BCoS was administered in hospital settings and at follow-up it was administered either in hospital, a rehabilitation clinic, Birmingham University or during a home visit. Examiners blind to the location of the stroke and the patient's condition performed both the initial and the follow-up testing. In this study we were interested in visuospatial attention deficits and based our analysis on 2 sub-tests: Apple cancellation (measuring different forms of neglect) and Visual Extinction (see below for details). To control for potential confounding factors, the analyses as described below also included demographic data (age, gender, handedness), type of stroke (ischemic, hemorrhage), the time between stroke and CT scan and the time between stroke and neuropsychological testing, the patient's awareness of their general setting and circumstance (the orientation questions assessed knowledge of personal information, awareness of time, place, medical condition and anosagnosia).

Neglect assessment. Neglect was assessed using the Apple Cancellation task (Bickerton et al., 2011; Chechlacz et al., 2010). This task is similar to the gap detection task by Ota et al. (2001) and is designed to simultaneously measure egocentric and allocentric neglect. Participants were presented with a page (A4) in landscape orientation with 50 apples presented across 5 invisible columns, one middle, one near left, one far left, one near right and one far right. Each column contained 10 complete apples (targets) along with distractors; the distractors were apples with either a left or a right part missing (incomplete apples; Fig 17A).

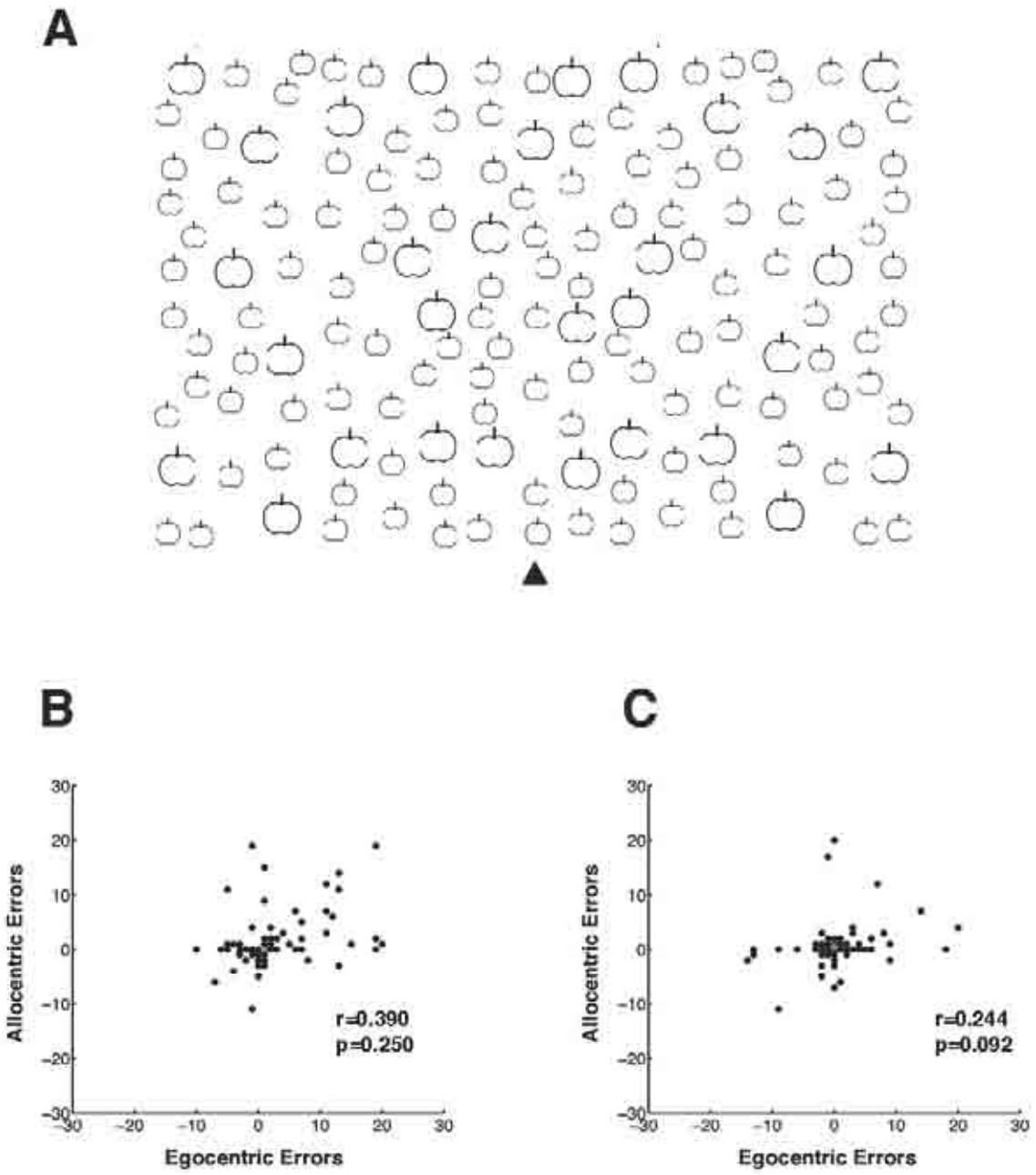

Figure 17. Example of the Apple cancellation task **(A)** used to simultaneously test for allocentric and egocentric symptoms. During this test patients are asked to cross all full apples. Egocentric neglect is measured by whether patients miss targets (full apples) predominantly on one side of the page and allocentric neglect is measured by whether patients make false positive responses by cancelling predominantly left or right distracters (according to the position of the gap defining a distracter; for full details and scoring see Methods section). Scatterplots of patientsÕegocentric neglect errors against patientsÕallocentric neglect errors on the Apple cancellation task at the subacute **(B)** and chronic **(C)** phase following stroke. There was no significant correlation between allocentric and egocentric neglect scores at both subacute and chronic phase. Please note that the middle grey dot corresponds to results for non-impaired patients.

Egocentric neglect is measured by whether patients miss targets (complete apples) on one side of the page. Allocentric neglect is measured by whether patients make false positive responses by cancelling distractors (i.e. incomplete apples) whose gap was on the left or right of the shape. In the neuroimaging analyses we used asymmetry scores for left and right allocentric (e.g., false alarms to distractors with a gap on the left – false alarms to distractors with a gap on the right) as well as normalized asymmetry scores for left and right egocentric neglect from the Apple Cancellation task (see Chechlacz et al., 2010 [Chapter 2], for details). The cut off scores for neglect were as follows: egocentric neglect - asymmetry for full apples <-2 right side errors or >3 left side errors; total numbers of target omissions i.e. accuracy score 40/50; allocentric neglect - asymmetry for incomplete apples (based on <2.5th percentile) <-1 right side errors or >1 left side errors. The cut-off for the total number of target omissions was 40/50; based on <2.5th percentile for patient performance (Chechlacz et al., 2010).

Visual extinction. The task consisted of 4 unilateral left, 4 unilateral right and 8 bilateral trials. Testing for visual extinction was done by the examiner raising his/her left and right index fingers on either side of his/her head and then moving (two brief bending movements) either left or right (unilateral trials) or both fingers simultaneously (bilateral trials). For each patient we calculated left and right asymmetry scores on two item trials and on unilateral trials. We also calculated, the left and right extinction index.

Extinction index: The difference in the asymmetry score on bilateral vs. unilateral trials was assessed, to index any spatially selective drop in response to two stimuli relative to the response to one stimulus. This was done separately for both left- and right-side items. To do this we calculated an extintion index i.e. the unilateral asymmetry score multiplied by two minus the bilateral asymmetry score, taking into account the difference in the number of

trials. The extinction index and the asymmetry score for both left- and right-side unilateral items were entered into the statistical models.

Each patient's behavioural performance was classified based on cut-offs drawn from the BCoS. Patients were classed as having a clinical deficit on measures of visual and tactile extinction if their scores on the task fell outside the control norms taken from 70 healthy controls without history of brain lesion or any neurological disorders. The cut off scores for tactile extinction task are as follows: unilateral trials (both left and right) <4 impaired; left bilateral trials <7 impaired; right bilateral participants younger than 74 years old < 8 impaired and participants older than 75 years old <7 impaired.

Neuroimaging assessment

Computed Tomography (CT) scans were acquired for all patients as part of their routine clinical assessment following stroke and hospital admission. The average time between suspected stroke and CT scan was 3.9 days (±10.2, with 93% of cases within a week). The neuroimaging data were acquired using the following scanners: Siemens Sensation 16, GE Medical System LightSpeed 16 and LightSpeed Plus. The images covered the whole brain with an in-plane resolution of 0.5 x 0.5 mm^2 and a slice thickness varying between 4-5 mm.

Neuroimaging analysis

Image preprocessing. Before the preprocessing stage, the quality of all CT scans was assessed by eye and all bad quality data sets (head movement or other image artefact) were removed. Subsequently, the remaining CT images were pre-processed using SPM8 (Statistical Parametric Mapping, Welcome Department of Cognitive Neurology, London UK). The

images were first normalized to an in-house CT template (Ashburner and Friston, 2003). The normalization was predominantly based on skull shape and was designed to transform the images into MNI space. In the next step we used the unified segmentation algorithm as implemented in SPM8 (Ashburner and Friston, 2005). In this unified model, the tissue class priors are encoded by de-formable tissue probability maps. The a-priori tissue class maps indicate the probability of finding expected signal sources of grey matter (GM), white matter (WM), cerebrospinal fluid (CSF), fat, bone and air (i.e. six different tissues classes), at each voxel of the image. As the CT scans were acquired following stroke, to account for the presence of an abnormal tissue associated with stroke, we adapted here a similar approach to Seghier et al. (2008) and included additional, seventh tissue class. Specifically, in the additional probability map we assumed that in each grey or white matter voxel there was a10% chance of it having a different intensity and thus representing an abnormal tissue class. In addition, we constrained the classification of GM and WM to each being based on a single Gaussian (normal) distribution, while two Gaussian distributions were used to model the intensities in the abnormal tissue class. This later procedure was used to account for any possible in-homogeneity of the abnormal tissue. CT images as opposed to MRI do not suffer from field bias due to field strength inhomogeneity, therefore we did not correct for that during pre-processing. In the final step of image pre-processing the segmented GM and WM images were smoothed with a 12-mm FWHM Gaussian filter to accommodate the assumption of random field theory used in the statistical analysis (Worsley, 2003). Finally, the quality of the segmentation and normalization procedures was assessed for each patient and images where the segmentation failed were removed from the analyses. The pre-processed GM and WM images were further used in the analyses to determine voxel-by voxel relationships between brain damage and visuospatial deficits (see below).

Voxel-based morphometry (VBM). We applied random effects analyses within the general linear model framework (Kiebel and Holmes, 2003) to compute correlations between the behavioral measures of visuospatial deficits at acute (Analysis 1) and chronic (Analysis 2) phase post stroke and the tissue damage (Ashburner and Friston, 2000). We used the full factorial design to generate models for GM and WM separately. The statistical models for Analyses 1 and 2 included the scores for both left and right allocentric and egocentric errors (extracted from the Apple Cancellation task) as assessed at acute and chronic phase post stroke respectively. This ensured that we could control and formally test for common and dissociated neuronal substrates that contribute to these two types of neglect. In all statistical models we also included four behavioural measures of other visuospatial problems: left and right asymmetry scores on unilateral trials and left and right visual extinction indices (extracted from the BUCS extinction test). This enabled us to examine the neuronal substrates of neglect symptoms with effects of other visuospatial deficits, which may co-vary with neglect, eliminated. Additionally, in the all statistical models age, gender, handedness, time from stroke to test (or time of BUCS follow up for Analysis 2), time from stroke to scan, the type of stroke (ischemia or hemorrhage) and 3 orientation measures were included as covariates of no interest.

Our neuroimaging analyses focused on left neglect symptoms since, as shown by our behavioural data, these symptoms were more frequent and more severe than the neglect symptoms after right hemisphere damage (see Table 15; this is in agreement with previous reports, for a review see Kerkhoff, 2001). However, we have not restricted our study to right hemisphere-lesioned patients and all statistical models included both left and right deficit scores. This was done to avoid biasing the results – for example, the exclusion of patients with left-hemisphere lesions could limit inferences about any potential contributions of the

affected brain regions to both left and right deficits.

The dissociation between left allocentric and left egocentric neglect was assessed by using exclusive masking, while common brain regions were tested using conjunction analysis (Nichols et al., 2005). Using the exclusive mask allowed us to identify damaged areas involved in left allocentric but not left egocentric neglect and vice versa (at the voxel level the threshold for the exclusive masking was $p<0.05$ uncorrected). To further verify the dissociations between allocentric and egocentric neglect, we report in the tables the results (F-tests) of the interaction between allocentric and egocentric neglect regressors. Common mechanisms were tested using conjunction analyses (Nichols et al., 2005) to highlight changes in voxel intensity that correlated with both left egocentric and left allocentric neglect at $p< 0.005$ uncorrected. We discuss only those results where there was a significant effect at $p< 0.001$ cluster-level corrected for multiple comparison with amplitude of voxels surviving of $p< 0.001$ uncorrected across the whole brain and an extent threshold of 200mm^3 (>100 voxels). The brain coordinates are presented in standardized MNI space. The anatomical localization of the lesion sites within the grey matter was based on the Anatomical Automatic Labeling toolbox (AAL toolbox, Tzourio-Mazoyer et al., 2002), the Duvernoy Human Brain Atlas (Duvernoy et al., 1991) and the Woolsey Brain Atlas (Woolsey et al., 2008). In order to localize white matter lesions associated with visual extinction in relation to specific white matter pathways we used the JHU White matter tractography atlas (Hua et al., 2008) and the MRI Atlas of Human White Matter by Mori et al. (2005).

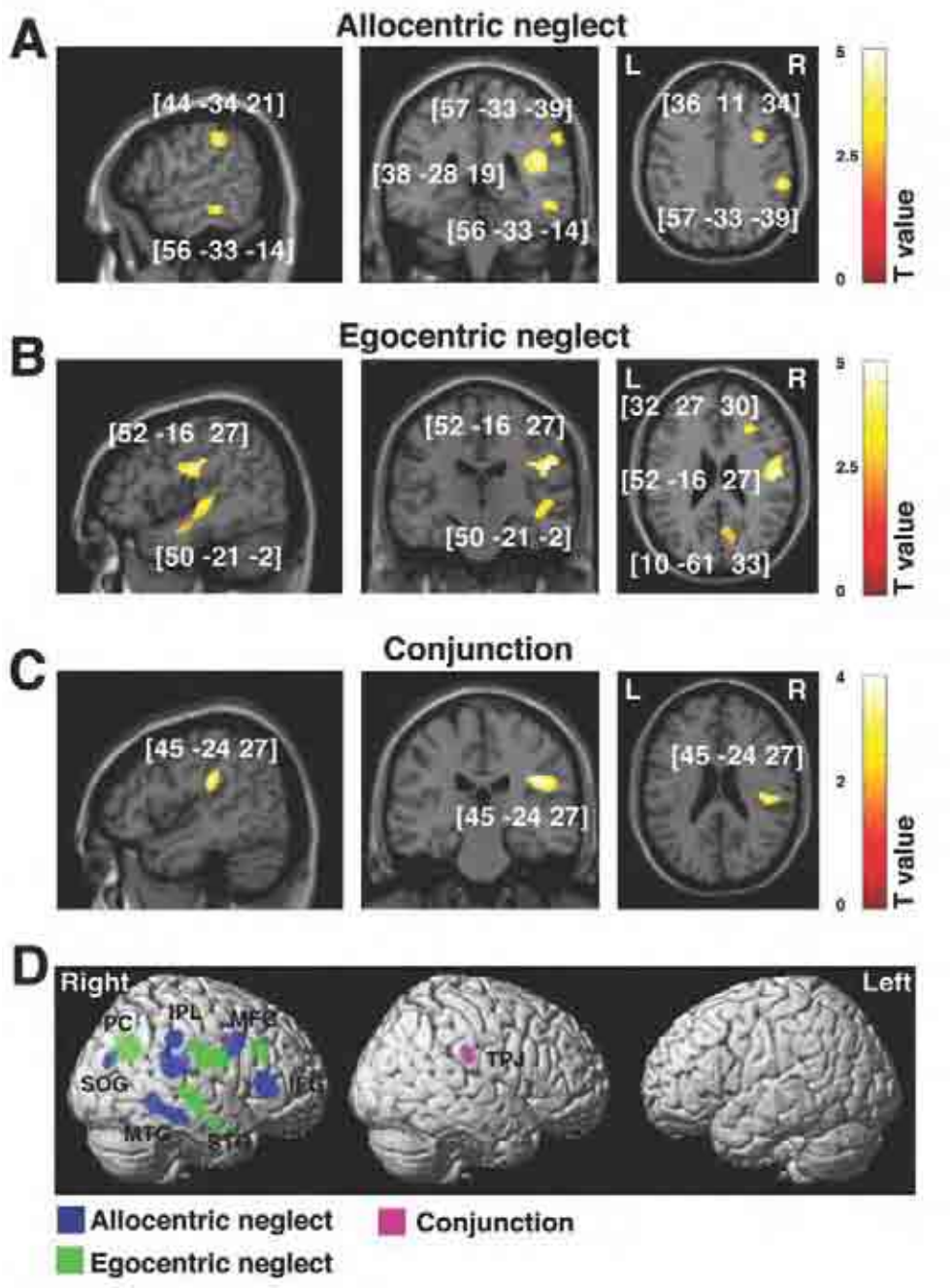

Figure 18. Voxel-wise statistical analysis of grey matter damage: allocentric versus egocentric neglect at the subcacute phase following stroke. VBM results showing voxels corresponding to grey matter damage in (**A**) left allocentric, (**B**) left egocentric and (**C**) both forms of neglect (conjunction analysis). Please note that in **A**, **B** and **C** the lesioned areas are coloured according to the significance level in the VBM analysis, where brighter colour means higher t-value. Numbers in brackets indicate peak MNI coordinates. **(D)** To further illustrate the relationship between grey matter loss associated with allocentric versus egocentric symptoms at the subacute phase, all clusters identified by VBM as described above are plotted on brain render. IFG, inferior frontal gyrus; IPL, inferior parietal lobule; MFG, frontal gyrus; MTG, middle temporal gyrus; PC, precuneus; STG, superior temporal gyrus; SOG, superior occipital gyrus; TPJ, temporal-parietal junction.

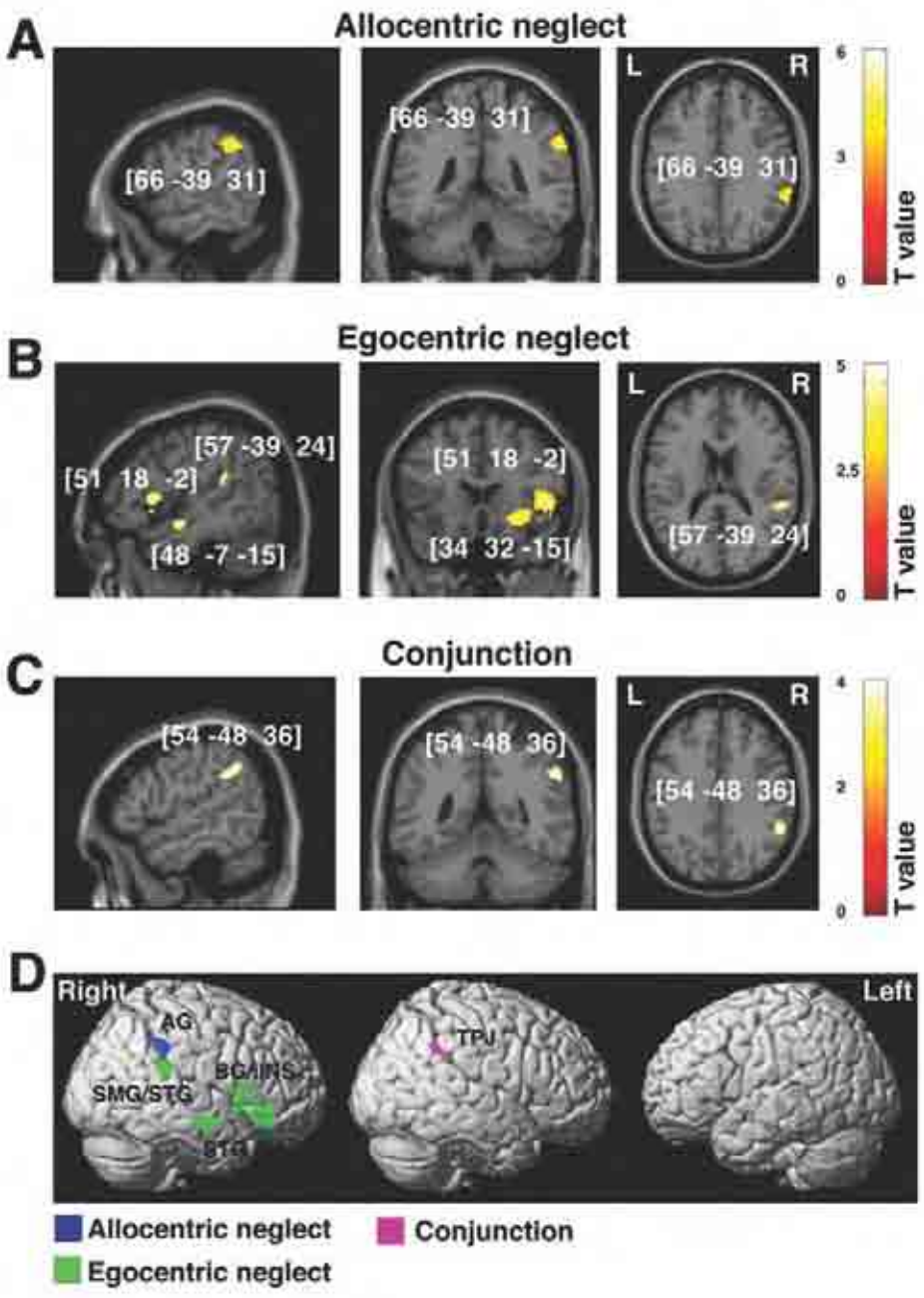

Figure 19. Voxel-wise statistical analysis of grey matter damage: allocentric versus egocentric neglect at the chronic phase following stroke. VBM results showing voxels corresponding to grey matter damage in (**A**) left allocentric, (**B**) left egocentric and (**C**) both forms of neglect (conjunction analysis). Please note that in **A**, **B** and **C** the lesioned areas are coloured according to the significance level in the VBM analysis, where a brighter colour means a higher t-value. Numbers in brackets indicate peak MNI coordinates. **(D)** To further illustrate the relationship between grey matter loss and any associated allocentric or egocentric symptoms at the chronic phase, all clusters identified by VBM as described above are plotted on a rendered brain. AG, angular gyrus; BG, basal ganglia; INS, insula; SMG, supramarginal gyrus; TPJ, temporal-parietal junction.

RESULTS

Table 15 presents demographic and clinical data for all the patients, including performance on the Apple Cancellation Task at both the subacute and chronic phases following stroke. Out of the 160 patients included in the current study, 15 patients at the subacute phase (<3 months) showed both left egocentric and left allocentric neglect, and 3 showed both right egocentric and right allocentric neglect with varied severity of impairments (assessed relative to control performance based on the Apple Cancellation Task). Interestingly, 3 patients showed left egocentric and right allocentric neglect, and 1 patient showed right egocentric and left allocentric neglect (see Humphreys and Riddoch, 1994a, 1995; Riddoch et al., 1995) for previous reports on the occurrence of allocentric and egocentric neglect on opposite sides of space within single patients). Furthermore, 13 patients exhibited left and 6 right egocentric neglect, and 6 patients exhibited left and 8 right allocentric neglect. Finally, 18 patients showed left visual extinction (4 of whom did not exhibit neglect), and 7 showed right visual extinction (6 of whom showed no neglect).

Subsequently, based on the behavioural findings and in agreement with previous reports we restricted our analyses to left neglect symptoms[15] but all statistical models included as additional regressors right egocentric and right allocentric errors as well as left and right visual extinction scores, to avoid biasing the results based on priori assumptions with regards to the neuroanatomy of the syndrome and to control for additional visuospatial problems associated with left neglect (see Methods section).

Out of the 15 patients who showed both left egocentric and left allocentric neglect at the subacute phase, 7 patients persisted in showing both deficits at the chronic phase while 7 patients recovered from both symptoms and 1 patient recovered from egocentric but not from

[15] As the patients included in our study predominantly suffered from unilateral left deficits we restricted further neuroimaging analyses to left unilateral neglect in order to achieve statistical significance.

allocentric neglect. Furthermore, out of 13 patients who exhibited only left egocentric neglect at the subacute phase, 9 persisted in showing egocentric symptoms, while 4 recovered. Out of the 6 patients who exhibited only left allocentric symptoms, 2 persisted in showing allocentric symptoms, while 4 recovered. Finally, of the 3 patients who showed left egocentric and right allocentric neglect at the subacute phase, 2 recovered from both symptoms and 1 persisted with only left egocentric symptoms. The patient who exhibited right egocentric and left allocentric neglect at a subacute phase recovered from egocentric but not allocentric symptoms.

Note that in the all analyses we used continuous scores for both types of neglect symptoms. By accounting for the severity of the symptoms and not just for their categorical presence, we attempted to provide a sensitive assessment of the relations between the two types of neglect. Using these continuous scores we could test for correlations between the severity of allocentric and egocentric neglect at both the sub-acute and chronic phases following stroke. Interestingly, there was no significant correlation between these two types of neglect at both the sub-acute ($r=0.390$ at $p=0.250$; Figure 17B) and chronic phases ($r=0.244$ at $p=0.092$; Figure 17C), supporting a dissociative account of the syndrome (see also Bickerton et al., 2011; Marsh and Hillis et al., 2008).

Grey matter: Acute vs. chronic prognosis of allocentric vs. egocentric symptoms

We used VBM based on the general linear model to investigate relationship between the grey matter substrates of sub-acute vs. persistent allocentric and egocentric symptoms of visual neglect. We demonstrated striking dissociations between the grey matter damage associated with both sub-acute and chronic allocentric neglect and egocentric neglect (Figure 18A,B and 19A,B; Table 16 and 17). When measured at the sub-acute stage, left allocentric

neglect was associated with right hemisphere lesions in frontal regions (the middle and inferior frontal gyri), the inferior parietal lobule partly extending into the superior temporal sulcus, and the middle temporal (partly extending into inferior temporal) and superior occipital gyri (Figure 18A, Table 16). In contrast, subacute left egocentric neglect was linked to damage to more anterior parts of the right hemisphere including the middle frontal gyrus, the postcentral gyrus extending into anterior part of supramarginal gyrus, the anterior and central superior temporal gyri and the precuneus (Figure 18B, Table 16).

The scans acquired at the sub-acute stage also predicted the substrates of persistent neglect at 9 months. The VBM analyses showed that although widespread lesions were associated with subacute neglect symptoms, only damage within a subset of the regions was critically associated with chronic neglect. Specifically, we found that lesions in the right hemisphere within the angular gurus were associated with persistent allocentric symptoms (Figure 19A, Table 17), while lesions within the superior temporal gyrus extending into the supramarginal gyrus were associated with persistent egocentric neglect (Figure 19B, Table 17). In addition, we found associations between chronic egocentric symptoms and lesioned voxels within the basal ganglia and insula (Table 17).

Importantly, our analysis also allowed us to test for substrates that are common for both types of neglect. The conjunction analysis revealed that damage within the right temporo-parietal junction (TPJ) was associated with both left allocentric and left egocentric errors on the Apple Cancellation Task and that lesions within this regions were critical for persistent symptoms (Figure 18C and Figure 19C, Tables 16-17).

Table 16. Grey matter substrates of subacute allocentric vs. egocentric neglect (VBM: Analysis 1).

Contrast	Cluster level		Voxel level			Coordinates			Brain Structure (location)
	P_{FWE}	Size	Z-score	Inter*	F(1,142)	X	Y	Z	
Left allocentric neglect*									
	0.000	928	4.84		3.75	**44**	**-34**	**21**	Right IPL (SMG and angular gyrus), STS
			4.38			38	-28	19	
	0.000	995	4.70		11.51	**34**	**30**	**6**	Right IFG
	0.000	114	4.17		5.17	**21**	**-78**	**24**	Right superior occipital gyrus
	0.000	661	4.12		5.80	**56**	**-33**	**-14**	Right MTG/ITG
	0.000	291	4.03		7.55	**57**	**-33**	**39**	Right angular gyrus/supramarginal gyrus
	0.000	521	3.92		5.97	**36**	**11**	**34**	Right MFG, sup precentral sulcus
Left egocentric neglect*									
	0.000	1069	4.69		9.21	**52**	**-16**	**27**	Right postcentral gyrus, supramarginal gyrus
	0.000	503	3.77		10.41	**32**	**27**	**30**	Right MFG
	0.000	1278	3.72		10.06	**10**	**-61**	**33**	Right precuneus
	0.000	572	3.67		4.04	**50**	**-21**	**-2**	Right STG
Common effect (conjunction analysis)									
	0.000	405	3.67			**45**	**-24**	**27**	Right TPJ

*To further verify the observed dissociations between allocentric and egocentric neglect, we report here the results (F-tests) of the interaction analyses between allocentric and egocentric neglect, these analyses directly test whether brain-behaviour correlations observed for allocnetric neglect are significantly higher than those observed for egocentric neglect, and vice versa. Abbreviations: IFG, inferior frontal gyrus; IPL, inferior parietal lobule; ITG, inferior temporal gyrus; MFG, middle frontal gyrus; MTG, middle temporal gyrus; STG, superior temporal gyrus; STS, superior temporal sulcus; TPJ, temporo-parietal junction.

Table 17. Grey matter substrates of chronic allocentric vs. egocentric neglect (VBM: Analysis 2).

Contrast	Cluster level		Voxel level			Coordinates			Brain Structure (location)
	P_{FWE}	Size	Z-score	Inter*	F(1,142)	X	Y	Z	
Left allocentric neglect*									
	0.000	494	5.13		5.39	**66**	**-39**	**31**	Right angular gyrus
Left egocentric neglect*									
	0.000	552	4.03		16.34	**34**	**32**	**-15**	Right BG (putamen), insula
	0.000	213	4.03		5.38	**51**	**18**	**-2**	Right insula
	0.000	400	3.94		15.11	**57**	**-39**	**24**	Right SMG, STG
	0.000	193	3.53		13.35	**48**	**-7**	**-15**	Right STG
Common effect (conjunction analysis)									
	0.000	318	3.27			**54**	**-48**	**36**	Right TPJ

*To further verify the observed dissociations between allocentric and egocentric neglect, we report here the results (F-tests) of the interaction analyses between allocentric and egocentric neglect, these analyses directly test whether brain-behaviour correlations observed for allocnetric neglect are significantly higher than those observed for egocentric neglect, and vice versa.
Abbreviations: SMG, supramarginal gyrus; STG, superior temporal gyrus; TPJ, temporo-parietal junction; VBM, voxel-based morphometry.

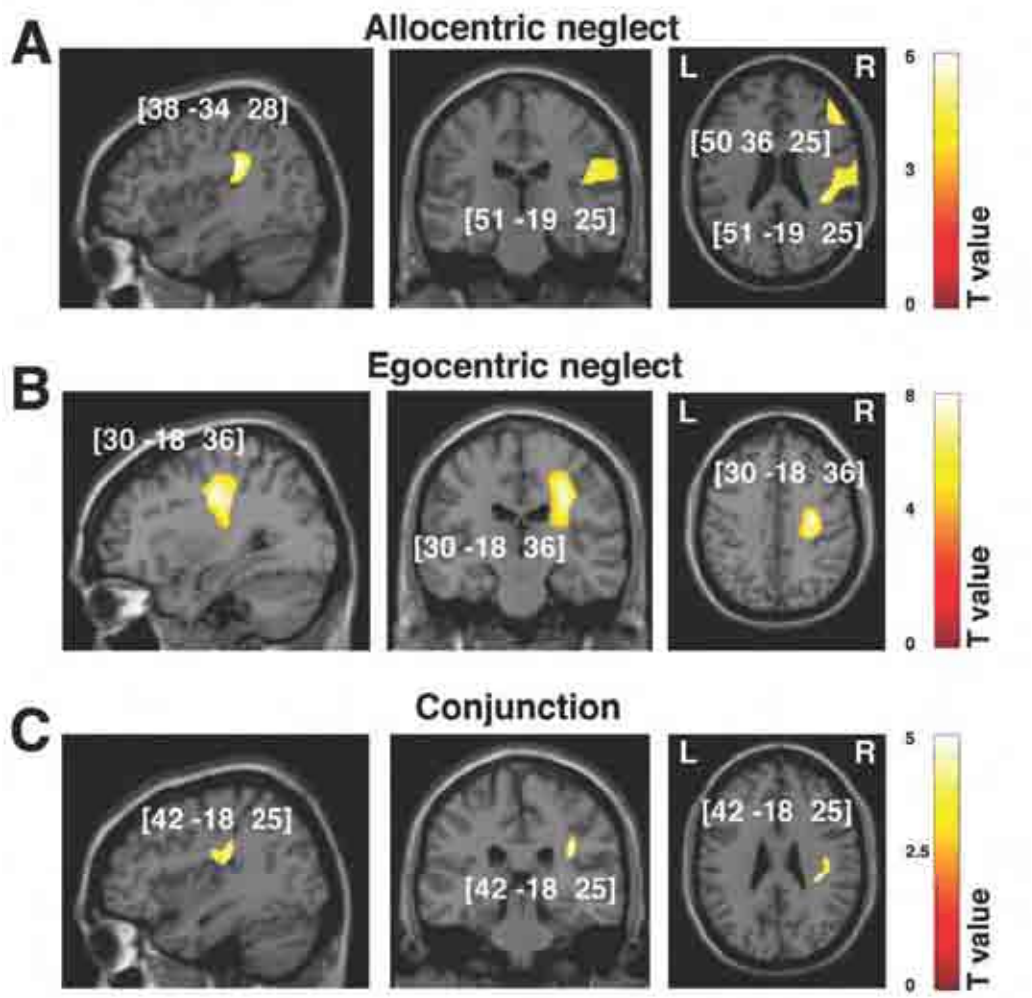

Figure 20. Voxel-wise statistical analysis of white matter damage: allocentric vs. egocentric neglect at the subacute phase following stroke. VBM results showing voxels corresponding to white matter damage in (**A**) left allocentric, (**B**) left egocentric and (**C**) both forms of neglect (conjunction analysis). Please note that in **A**, **B** and **C** the lesioned areas are coloured according to the significance level in the VBM analysis, where brighter colour means higher t-value. Numbers in brackets indicate peak MNI coordinates.

White matter: Acute versus chronic prognosis of allocentric versus egocentric symptoms

Similar to the assessments of grey matter damage we used VBM analyses to co-vary out allocentric and egocentric components of visual neglect at the sub-acute and chronic phases following stroke. These analyses demonstrated that disconnections resulting from damage along the right superior longitudinal fasciculus (SLF) were associated with both types

of neglect symptoms and related to both subacute and chronic deficits (Tables 18-19, Figure 20 and 21). This was further confirmed by VBM-based conjunction analyses, although the results only reached significance threshold for analyses of sub-acute deficits and were marginal for the common effect of persistent neglect symptoms (Table 19). Furthermore, we showed that damage within the anterior part of the inferior fronto-occipital fasciculus (IFOF) and the uncinate fasciculus were associated with both types of neglect symptoms, while damage within inferior longitudinal fasciculus (ILF), superior corona radiata and superior thalamic radiations was associated with egocentric neglect. Disconnections within these additional long association pathways were critical for both sub-acute and chronic neglect symptoms (Tables 18-19; Figure 20 and 21).

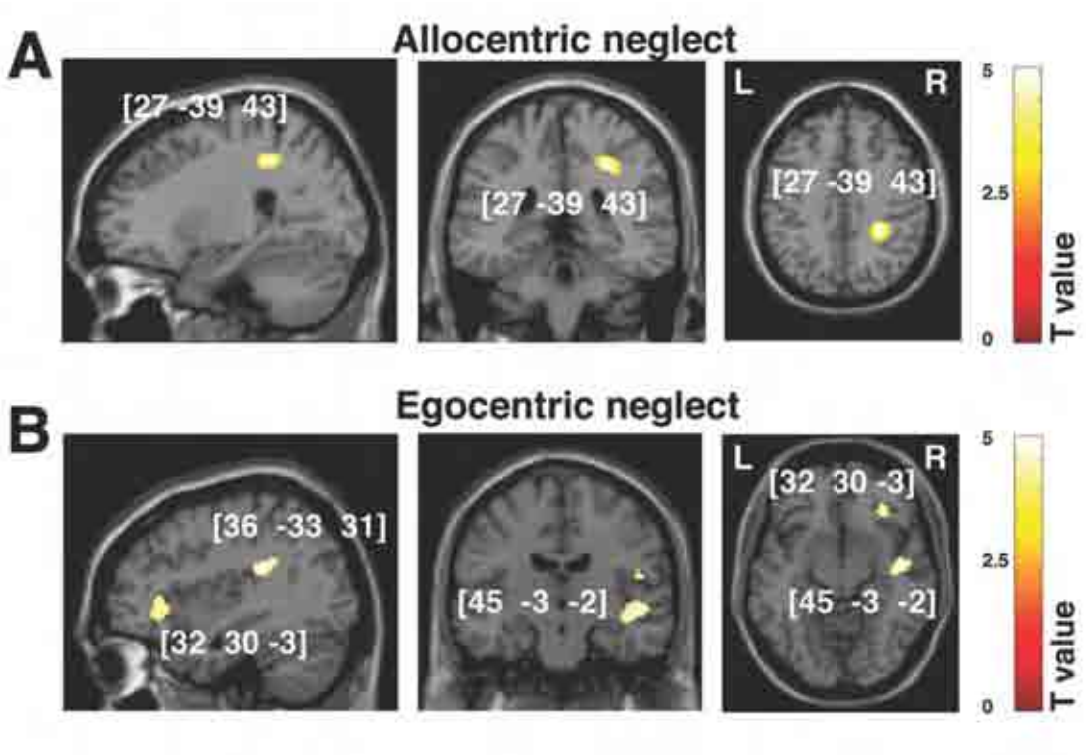

Figure 21. Voxel-wise statistical analysis of white matter damage: allocentric vs. egocentric neglect at the chronic phase following stroke. VBM results showing voxels corresponding to white matter damage in (**A**) left allocentric, (**B**) left egocentric neglect. Please note that in **A** and **B** the lesioned areas are coloured according to the significance level in the VBM analysis, where brighter colour means a higher t-value. The numbers in brackets indicate the peak MNI coordinates.

DISCUSSION

The current study examined whether information gained from computed tomography scans acquired as a part of routine clinical diagnosis following stroke has the potential to predict recovery vs. persistent symptoms associated with heterogeneous visuospatial neglect symptoms. Our data support a dissociative account of egocentric and allocentric neglect both in terms of the distinct behavioural deficits and the associated neuronal substrates (Hillis et al., 2005; Chechlacz et al., 2010 [Chapter 2]; Medina et al., 2009). Importantly, our findings indicate that the substrates of persistent neglect can be predicted from clinical scans acquired sub-acutely following stroke. We showed that lesions in the angular gyrus were associated with persistent allocentric symptoms, while lesions within the superior temporal gyrus extending into the supramarginal gyrus, as well as damage to the basal ganglia and insula, were associated with persistent egocentric neglect. Furthermore, we found that that damage within temporo-parietal junction (TPJ) and white matter disconnections resulting from damage along the superior longitudinal fasciculus were critically link to the persistent presence of both types of neglect. Bickerton et al. (2011) reported that patients with both types of neglect tended to have a worse functional outcome at 9 months than patients with only egocentric or only allocentric neglect, and that the presence of both sets of symptoms was additionally linked to the presence of depression. The present analysis suggests that the poor outcomes are linked to the presence of damage to the right TPJ as well as proximal white matter.

These findings are in direct agreement with our previous work into the neural correlates of allocentric and egocentric errors on Apple Cancellation Task in chronic brain injury patients (Chechlacz et al., 2010 [Chapter 2]). Specifically, both analyses point to damage to chronic allocentric problems being linked to the angular gyrus while chronic

egocentric symptoms are associated with damage within the supramarginal and superior temporal gyri and the basal ganglia. Yet again, this work supports the argument that distinct cortical regions control attention across space and attention within objects ('between' and 'within object' spatial representations; see Humphreys, 1998), while common cortical regions (mainly the right TPJ), and common white matter pathways (mainly the SLF), support attention to both spatial and object-based representations (see Chechlacz et al., 2010). Alternative accounts of the distinction between egocentric and allocentric neglect can also be offered. One is that egocentric neglect reflects a problem in global space perception while allocentric neglect reflects a problem in representing space at a more local scale. Halligan and Marshall (1994) proposed that left neglect after right hemisphere damage is brought about by the combination of poor global space perception along with a spatial bias in attention. In the Apples test of neglect, poor global perception could lead to patients not attending to one side of the page. Poor attention to local spatial areas is associated with left rather than right hemisphere damage (Delis et al., 1983) and, if coupled to a spatial bias in selection, then there may be poor detection of missing parts on one side of individual objects – what we have labelled as allocentric neglect. However we found no evidence that allocentric neglect was associated with left hemisphere damage, as might be expected on this account. In addition, the Apples test uses both large and small apples, which may correspond to global and more local representations, but there was no evidence for any bias based on the sizes of the stimuli. A further possibility is that both forms of neglect stem from a gradient of attention across egocentric space (e.g., Driver and Pouget, 2000). On this gradient account, there will be a bias against elements on one side of objects, even when the objects fall in the ipsilesional visual field. Again, this account has problems with the data. For example, it predicts that allocentric and egocentric neglect should co-occur behaviourally and they should be underpinned by

common lesion sites. In contrast to this the behavioural data here indicate dissociations between patients with one or other form of neglect and, in addition, egocentric and allocentric neglect are associated with contrasting lesions. This gradient account also fails to explain prior results where opposite egocentric and allocentric biases have occurred even in the same patient, which also arose in some cases in the present sample (Humphreys and Riddoch, 1994a, 1995).

The current study demonstrated that the anatomical distinctions between the different forms of neglect arose not only at the sub-acute phase but also at the chronic phase following stroke. This matches the data from imaging at the chronic stage (Chechlacz et al., 2010 [Chapter2]). However, it should be also noted that, in comparison to our previous work, the current study identified a more confined network of cortical and sub-cortical regions associated with chronic neglect. This could be explained by the fact that, in contrast to Chechlacz et al (2010), the neural substrates of chronic deficits were examined here using scans acquired at a sub-acute phase. Consequently, we were unable to take into account additional brain damage in chronic cases which may result from secondary infarcts/degeneration in cortical regions that were initially structurally intact but affected by perfusion abnormalities (Butcher et al., 2003; Rivers et al., 2006; Thomalla et al., 2004; Werring et al., 2000). Thus, if anything, our analyses provide an underestimation of the contribution of lesions to chronic neglect symptoms due to potential delayed infarction following stroke.

Persistent neglect is associated with overall poor functional outcome following stroke (Bickerton et al., 2011; Buxbaum et al., 2004; Cherney et al., 2001). Previous work suggests that the initial severity of deficits, the presence of visual field defects, the age at which the lesion occurred and the presence of age-associated brain atrophy are useful indicators of

recovery in addition to lesion size and location (Campbell and Oxbury, 1976; Gottesman et al., 2008; Stone et al., 1992; Farne et al., 2004; Cherney and Halper, 2001; Kertesz and Dobrowolski, 1981; Levine et al., 1986; Cassidy et al., 1999; Samuelsson et al., 1997). The current study however shows that lesion location alone can serve as a critical predictor for persistent neglect symptoms even when the other factors are co-varied out in the analysis. This sets our study apart from the previous work (e.g., Karnath et al., 2011 where only the severity of neglect has been controlled.

Samuelson et al (1997) first reported that lesions in white matter under temporo-parietal junction were highly correlated with persistent neglect. These findings are consistent with damage within the SLF. Importantly, our white matter analyses also indicated that damage within SLF, in addition to other long association pathways, was critically associated with persistent neglect symptoms. The SLF is the main component of the attention network connecting temporo-parietal association areas with the frontal lobes (Bartolomeo et al., 2007; Makris et al., 2005; Petrides and Pandya, 2006; Schmahmann and Pandya, 2006). Many previous studies have link disconnections resulting from damage within SLF to unilateral neglect (Chechlacz et al., 2010 [Chapter 2]; He et al., 2007; Thiebaut de Schotten et al., 2008), but without showing that damage at the sub-acute stage predicts longer-term recovery, as we do here. The current results are consistent with information from both between- and within-object representations of space being conveyed through common pathways to frontal brain regions concerned with action (see Corbetta and Shulman, 2002; Humphreys, 1998). The present paper shows that it is possible to conduct lesion-symptom mapping using clinically-acquired CT scans, and this can complement research-based scanning using high-resolution MRI. This indicates that it may be possible to use clinical scans to predict outcome for individual patients. There are however some potential limitations. First, it is known that

lesions resulting from ischemic stroke may be underestimated when CT scans are taken early-on after a stroke (Wardlaw and Farrall, 2004). Secondly, CT scans fail to detect cortical dysfunction within a region that is structurally intact but has inadequate cortical perfusion, and this dysfunction may contribute to cognitive deficits. The second point is particularly critical as previous reports have link cortical malperfusion to deficits in spatial attention (e.g. Hillis et al., 2000a; Hillis et al., 2005; Karnath et al., 2005; Ticini et al., 2010). Despite these limitations, though, the current study indicates that the site of damage, revealed by semi-automated analysis of clinical scans, can help predict the long-term presence of different forms of unilateral neglect.

Conclusions and clinical implications

The present study examined the neuroanatomy of subacute relative to chronic neglect and whether persistent neglect symptoms could be predicted based on clinical CT scans acquired at the stroke diagnosis. Despite the fact that computed tomography have limitations resulting in potential underestimation of tissue damage, our findings strongly indicate that these scans can be applied to predict neglect recovery versus persistent symptoms and thus provide information central to patients clinical care. Specifically, we found that lesions in the angular gyrus were associated with persistent allocentric neglect, while damage within the STG extending into the supramarginal gyrus, as well as lesions within the basal ganglia and insula, were associated with persistent egocentric neglect. Furthermore, damage within the TPJ was associated with both types of persistent neglect symptoms. As previously discussed many different factors such as the initial severity of symptoms, the presence of visual field defects, the age at which the lesion occurred and the presence of age-associated brain atrophy have been designated as predictors of neglect recovery but the results have been varied and

often contradictory (e.g., Campbell and Oxbury, 1976; Gottesman et al., 2008; Stone et al., 1992; Farne et al., 2004; Cherney and Halper, 2001; Kertesz and Dobrowolski, 1981; Levine et al., 1986; Cassidy et al., 1999; Samuelson et al., 1997). Importantly, our work and two other recent studies strongly indicate that neuroimaging data enabling estimation of the lesion size (extent of tissue damage) and even more importantly lesion location are needed to fully evaluate potential for recovery in individual patients (Karnath et al., 2011; Khurshid et al., 2011). The neglect symptoms are heterogeneous and the severity of cognitive deficits observed in individual patients at acute and subacute phase following stroke depends on several different functional aspects. For example the extent of visuospatial impairments characteristic of neglect may be exacerbated by deficits in non-spatial cognitive process (Singh-Curry and Husain, 2010). Thus, information about lesion location and understanding the neuroanatomy associated with specific symptoms are key in evaluating cognitive deficits of individual patients and it can be speculated that the clinical computed tomography scans used to assess lesion location are more predictive than clinical neuropsychological scores to predict functional outcome i.e. neglect recovery versus persistent symptoms. However, as the contribution of both visuospatial and non-spatial cognitive deficits to heterogeneous neglect symptoms varies in individual patients, extensive neuropsychological evaluation combined with information about underlying lesion anatomy is required to not only fully understand potential for recovery but also to design effective rehabilitation geared towards needs of individual patients. Importantly, our findings point towards the possibility of development of clinically useful tools for predicting stroke functional outcomes from computed tomography scans utilizing statistical modelling of data based on either machine learning approaches using pattern recognition methods or classification algorithms using logistic regression models (for examples of previous attempts of using neuroimaging data to predict stroke outcome see Phan

et al., 2010; Reid et al., 2010; Saur et al., 2010). In the past the machine learning and classification algorithm methods have been mostly used to neuroimaging modalities other than computed tomography. Nevertheless, the advantage of CT scans is that these are commonly used in clinical settings and provide direct representation of tissue density. Furthermore, as the presented here findings strongly advocate the potential of using CT data to predict functional recovery, we conclude that the use of this imaging modality to develop novel tools for making meaningful predictions of clinical outcome following stroke presents an attractive and feasible possibility.

Table 18. White matter substrates of acute/subacute allocentric vs. egocentric neglect (VBM: Analysis 1).

Contrast	Cluster level		Voxel level			Coordinates			Brain Structure (location)
	P_{FWE}	Size	Z-score	Inter*	F(1,142)	X	Y	Z	
Left allocentric neglect*									
	0.000	703	5.94		4.71	**60**	**18**	**10**	Right IFOF, UNC
			5.30			50	36	25	
	0.000	2142	5.93		21.33	**38**	**-34**	**28**	Right SLF
			4.85			51	-19	25	
Left egocentric neglect*									
	0.000	2821	7.11		60.57	**30**	**-13**	**36**	Right SLF, sup CR; sup TR
Common effect (conjunction analysis)									
	0.000	389	4.47			**42**	**-18**	**25**	Right SLF

*To further verify the observed dissociations between allocentric and egocentric neglect, we report here the results (F-tests) of the interaction analyses between allocentric and egocentric neglect, these analyses directly test whether brain-behaviour correlations observed for allocnetric neglect are significantly higher than those observed for egocentric neglect, and vice versa.
Abbreviations: IFOF, inferior fronto-occipital fasciculus; SLF, superior longitudinal fasciculus; sup, superior; TR, thalamic radiation; UNC, uncinate fasciculus; VBM, voxel-based morphometry.

Table 19. White matter substrates of chronic allocentric vs. egocentric neglect (VBM: Analysis 2).

Contrast	Cluster level		Voxel level			Coordinates			Brain Structure
	P_{FWE}	Size	Z-score	Inter*	F(1,142)	X	Y	Z	(location)
Left allocentric neglect*									
	0.000	508	4.89		7.61	**27**	**-39**	**43**	Right IFOF, SLF
Left egocentric neglect*									
	0.000	924	4.54		22.29	**32**	**30**	**-3**	Right IFOF, UNC
	0.000	1194	4.46		22.16	**45**	**-3**	**-2**	Right ILF, SLF
			4.32			48	-9	10	
	0.000	280	4.45		21.00	**36**	**-36**	**25**	Right SLF, post TR
Common effect (conjunction analysis)**									
	1.000	21	2.81			**36**	**-33**	**31**	Right SLF

*To further verify the observed dissociations between allocentric and egocentric neglect, we report here the results (F-tests) of the interaction analyses between allocentric and egocentric neglect, these analyses directly test whether brain-behaviour correlations observed for allocnetric neglect are significantly higher than those observed for egocentric neglect, and vice versa.**Not significant.
Abbreviations: IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; post, posterior; SLF, superior longitudinal fasciculus; TR, thalamic radiation; UNC, uncinate fasciculus; VBM, voxel-based morphometry.

CHAPTER 6:

GENERAL DISCUSSION

"To pay attention, this is our endless and proper work."

(Mary Oliver, Yes! No! from Owls and Other Fantasies, 2003)

SYNOPSIS

The world around bombards us with a large amount of visual information and different elements within the visual scene compete for our attention and the allocation of limited processing resources. For successful survival we need to be able to not only select and process a subset of behaviourally relevant visual stimuli while ignoring the rest of visual scene, but also to effectively shift attention between different elements/locations within the visual scene. The underlying cognitive processes that underlie these abilities are collectively known as visuospatial attention. The complex cognitive mechanisms involved are indispensable for simple daily activities, and this is illustrated by the profound behavioural deficits and problems experienced by individuals suffering from visuospatial syndromes after brain lesion, including unilateral neglect, extinction and simultanagnosia. For example patients with neglect might ignore food on one half of their plates as they lack of spatial awareness of one side of space, while patients with simultanagnosia might frequently bump into things surrounding them as they perceive the world as a random compilation of objects without having any spatial frame of reference. These disorders have proven to be difficult to both understand and treat (e.g. Parton et al., 2004; Rizzo and Vecera, 2002; Singh-Curry and Husain, 2010). Much research effort has been given over to exploring the neuronal mechanisms associated with these syndromes. The work presented in this thesis aimed to further explore the structural and functional organization of human visuospatial attention network by decomposing the neuroanatomy of unilateral neglect, extinction and simultanagnosia. The empirical chapters presented here clearly demonstrate that different

patterns of grey matter lesions, as well as the laterality of white matter disconnections in individual neuropsychological patients, is key to understanding the attentional processes which are disrupted, and thus the nature of cognitive symptoms observed in patients. Furthermore, the novel findings presented here provide strong evidence that lesion-symptom mapping studies, far from being a relict of past research, provide important insights into our understanding of human cognition.

OVERVIEW OF THE FINDINGS AND GENERAL CONCLUSSIONS

The visuospatial disorders examined in this thesis, unilateral neglect, extinction and simultanagnosia, often co-occur. Furthermore individual patients frequently present with heterogeneous symptoms associated with a single disorder. This can clearly make it difficult to study neuropsychological deficits. Moreover, previous reports have often failed to take into account the complexity of deficits, tending instead to treat all patients within a syndrome as a homogeneous group – with consequent clouding of any interpretation. Here an approach was taken to attempt to fractionate within broad syndromes, such as visual neglect, in order to derive a clearer understanding of lesion-symptom relations, while at the same time controlling for other factors that can co-vary across patients. Where this was not possible due to small group numbers (e.g., with simultanagnosia), the work provides the first-ever analysis of the underlying neural substrates, and so makes a contribution even without full behavioural fractionation.

Neuronal substrates of neglect, extinction and simultanagnosia

The first empirical chapter (Chapter 2, Chechlacz et al., 2010) in this thesis aimed to decompose the neural substrates of different symptoms associated with the syndrome of

visual neglect, specifically the contributions of common and dissociable grey and white matter changes underlying allocentric and egocentric symptoms. I argued that these two symptoms of unilateral neglect represent deficits in different dimensions of spatial attention, across space in relation to the body (egocentric neglect) and across parts within objects (allocentric neglect). Prior lesion-symptom mapping studies in neglect have been somewhat controversial with different research groups having strong but diverse opinions. Specifically, some groups have argued that neglect is linked to relatively anterior damage (including the superior temporal gyrus and insula; see for example Karnath et al., 2001; Karnath et al., 2004), while others have argued that neglect is linked to posterior parietal cortex lesions (Mort et al., 2003). The aim of the work presented in Chapter 2 was to resolve this ongoing debate with a novel analysis of both white and grey matter lesions associated with different symptoms of visual neglect, using continuous behavioural scores and voxel-wise methods based on segmented grey and white matter tissue. In addition, voxel-based lesion-symtpom mapping was combined with diffusion tensor imaging, to gain a more accurate analysis of any contributions from damage to specific fibre tracts. The results offered an elegant resolution for these controversies by showing dissociated and overlapping grey and white matter structures that are associated with the heterogeneous neglect syndrome and thus provided interesting insights into the neuronal networks necessary to the allocation of attention to space. Furthermore, this work added to the growing body of evidence (e.g. Hillis et al., 2005; Medina et al., 2009; Verdon et al., 2010) showing dissociations between the neural bases of different neglect symptoms. Specifically, the results here indicated contrasting regions of cortical damage linked to egocentric and allocentric neglect. Most notably, allocentric symptoms were associated with more posterior damage (the posterior superior temporal sulcus, the angular, middle temporal/inferior temporal and middle occipital gyri) than

egocentric symptoms (linked to the middle frontal, postcentral, supramarginal and superior temporal gyri as well as the insula). In addition to the distinct sites of grey matter damage, lesions within the intraparietal sulcus and the temporo-parietal junction were associated with both forms of neglect. Finally, there were common white matter lesions across the two neglect symptoms - in particular damage was found within the SLF, ILF, IFOF, the thalamic radiation and the corona radiata. These findings supported previous reports linking neglect to structural disruption of connectivity within the visual attention network, linked to damage within long association pathways (Bartolomeo et al., 2007, Urbanski et al., 2008; Bird et al., 2006; He et al., 2007; Thiebaut de Schotten et al., 2005). In summary, this work not only fractionated different neglect symptoms but also demonstrated that distinct cortical regions control attention across space and within objects, while common cortical regions (TPJ, IPS) and common white matter pathways support interactions across these different cortical regions.

The results presented in Chapter 2 (Chechlacz et al., 2010) also argued against alternative accounts of visual neglect. For example, one possibility is that egocentric and allocentric neglect symptoms reflect the processes of attending to global and more local representations of space (Halligan and Marshall, 1994a). Note however that poor attention to the global aspects of space is associated with damage to the right hemisphere while attention to local stimuli has been linked to left hemisphere damage (Delis et al., 1986). Contrary to this, there was no evidence that allocentric neglect, possibly linked to poor attention to local objects, was associated with left hemisphere damage. Another counter argument is that egocentric and allocentric neglect both stem from a single graded lesion of attention across a common, egocentric spatial representation. The graded nature of the lesion can lead to relatively better performance on the ipsi- relative to the contralesional side of objects even when they fall in the ipsilesional field (Driver and Pouget, 2000). However this account

predicts that egocentric and allocentric neglect should co-occur and be reflected in common patterns of lesions. The behavioural and neuroanatomical dissociations reported here contradict this.

While Chapter 2 was concerned with contrasting the neural substrates of unilateral neglect, the next two chapters decomposed the relationship between the neuroanatomy of different but nevertheless often co-occurring spatial attention syndromes. First, Chapter 3 (Chechlacz et al., 2012) explored the patterns of lesions linked to visual and tactile extinction, as well as those related to visual field defects and egocentric (spatial) neglect. Similarly to Chapter 2, the analyses used both continuous behavioural scores and continuous anatomical information entered into statistical analyses based on VBM. This approach sets the study apart from previous reports, which have examined mainly single components of visuospatial attention and/or have used all-or-none classifications of deficits in patients (e.g. Karnath et al., 2003; Ticini et al., 2010). The present approach evaluated whether there were both common and distinct structure-function relationships for extinction rather than neglect across the whole brain. The analysis was also undertaken separately for grey and white matter and based on continuous behavioural measures in order to take into account that extinction is typically not an all-or-none phenomenon and thus may reflect in individual patients the relative competition between contra- and ipsilesional stimuli. The results presented evidence for both common and distinct neural substrates associated with neglect and extinction, across both visual and tactile modalities. These findings potentially explain why some patients experience symptoms of both disorders, while dissociations have been also reported across different individuals (e.g. Manes et al., 1999; Ress et al., 2000; Vuilleumier and Rafal, 2000). Specifically, damage to the angular gyrus, the superior temporal sulcus, the middle occipital gyrus and the insula were linked to extinction, while lesions involving the supramarginal

gyrus (SMG), the IPS, the middle frontal and the superior temporal gyri (STG) were associated exclusively with egocentric neglect. The results further demonstrated that damage to the TPJ, the middle temporal gyrus, the insula and putamen generated both visual extinction and neglect. These findings are in direct agreement with results presented in Chapter 2 as well as other reports indicating central role of the STG and SMG in egocentric neglect (Chechlacz et al., 2010 [Chapter 2], Karnath et al., 2004, Medina et al., 2009). Interestingly, the data in Chapter 2 indicate that allocentric neglect was associated with damage to the regions similar to these associated with extinction based on the results in Chapter 3 (Chechlacz et al., 2012). This in turn suggests that these similar regions are involved in balancing visuospatial resources given to the left and right locations being processed simultaneously in object recognition. However these findings may need to be considered with caution as other reports point out to the middle temporal gyrus coding the left and right sides of individual objects irrespective of their position in the visual field (Committeri, et al., 2004; Khurshid et al., 2011). Thus, the question whether measuring extinction reflects the relative rather than absolute positions of the stimuli attended to remains to be examined. Finally, the findings also demonstrated the central role of the temporo-parietal junction and the superior longitudinal fasciculus in supporting multi-item competition and attentional biases in visuospatial selection. These important and novel findings support the data presented in Chapter 2. Subsequently, the main conclusions were that (i) the TPJ within each hemisphere plays a role in the competitive interactions across space that determine the identification of multiple items, briefly presented across different modalities and (ii) the SLF seems necessary to support interactions between functionally specialized regions involved in attentional control across different sensory modalities.

The third study decomposing the neuroanatomy of different visuospatial disorders

focused on simultanagnosia (Chapter 4, Chechlacz et al., 2011). The pattern of lesion, the lesion volume and laterality were examined using advanced brain imaging methods, including diffusion tensor imaging and high resolution structural MRI. For the first time, a group of seven simultanagnosia patients was assembled and contrasted with control neuropsychological patients. This particular work delineated the critical lesions associated with simultanagnosia, their relations to the behavioural symptoms, and the overlap with other spatial disorders - notably neglect and extinction (see also Rizzo and Vecera, 2002 for a review). The critical lesions for simultanagnosia were linked to the parieto-occipital and middle occipital regions as well as to the middle frontal area (BA46), while lesions within the temporo-parietal junction and the inferior parietal lobule (angular gyrus) were associated with unilateral visuospatial symptoms. These results are in agreement with previous reports examining the neuronal substrates of neglect and extinction (e.g., Verdon et al., 2010; Medina et al., 2009, Karnath et al., 2004; Ticini et al., 2010; see also Chapters 2 and 3 [Chechlacz et al., 2010; Chechlacz et al., 2012) and with single case reports of simultanagnosia (e.g. Clavagnier et al., 2006; Rizzo and Hurtig, 1987). Strikingly, the findings presented in Chapter 4 (Chechlacz et al., 2011) demonstrate that bilateral parieto-occipital white matter disconnections are both distinctive and necessary to create the symptoms associated with simultanagnosia. The analysis of white matter damage based on DTI tractography revealed associations with bilateral lesions to major pathways within the visuospatial attention network, including the SLF, IFOF and ILF. This study constitutes the first comprehensive analysis of lesion-symptom relations in simultanagnosia while also making critical contrasts between simultanagnosia itself and associated deficits, such as unilateral neglect and extinction. The main findings, highlighting the role of severe white matter disconnections, contribute to the understanding of the functional underpinnings of simultanagnosia. At a

functional level, the data are consistent with Duncan et al.'s (2003) argument linking simultanagnosia to severe impairments in visual processing speed.

Neuroanatomy of visuospatial syndromes: conclusions and final remarks

Taken together, the findings presented in the first three empirical chapters of the thesis (Chapters 2-4), as reviewed above, provide new and important insights into the functional organization of the interconnected networks underlying visuospatial attention. The results provide strong evidence (i) about functional specializations within the visuospatial attention network based on both common and distinct neuronal substrates of different syndromes and (ii) that different patterns of grey matter lesions, and the laterality of white matter disconnections in individual neuropsychological patients, determines the degree to which visual processing and spatial attention are disrupted, and thus the nature of visuospatial deficits. The data highlight that cortical regions including the middle frontal, supramarginal and superior temporal gyrus control attention across space while the angular gyrus and middle temporal gyrus control attention within objects. In addition, common cortical regions (notably around the temporo-parietal junction) and common white matter pathways support interactions across these different cortical regions. Furthermore, the data demonstrate that the profound deficits in visual attention and visual selection that characterise simultanagnosia are linked to grey matter damage within the middle frontal, parietal (intraparietal and postcentral gyri) and occipital (parieto-occipital fissure, cuneus and calcarine) cortices, along also with bilateral parieto-occipital white matter disconnections. These neuroanatomical deficits result in poor visual processing of multiple objects, striking deficits in the ability to select low saliency stimuli and the loss of processing speed characteristic of this disorder.

The findings presented here highlight the roles of several different brain regions

involved in visuospatial attention but one of these regions merits special consideration - the temporo-parietal junction. Lesions within the right TPJ have been traditionally associated with unilateral neglect (Vallar and Perani, 1986; see also Chechlacz et al., 2010 [Chapter 2]), but the extensive evidence presented here points to particular role of this region in visual selection. One proposal (e.g., Mavritsaki et al., 2010) is that the TPJ acts as a form of saliency map that promotes shifts of attention to behaviourally relevant items. Thus damage to the right TPJ would lead to spatial biases in selection as found in both neglect and extinction (as demonstrated in my thesis). In patients with neglect stimuli falling on the contralesional side of the map may have reduced saliency relative to those appearing on the ipsilesional side, which means that the contralesional items may not be inspected. In patients with extinction, the saliency map might be activated enough to enable a unilateral stimulus to be detected, but either competition within the map or a lack of feedback from the map would lead to an attentional disadvantage for contralesional stimuli when competing with ipsilesional stimuli under conditions of brief presentation (Riddoch et al., 2010). Furthermore, data presented in my thesis suggests that the salience-detection function of the TPJ is bilateral, given that damage to the TPJ is associated with allocentric as well as egocentric neglect, though the right TPJ may play a more dominant role (see also Corbetta and Shulman, 2002; Mavritsaki et al., 2010). It should be noted that a recent fMRI study in healthy controls also provides evidence supporting the role of both the left and right TPJ, rather than the right TPJ alone, in attentional orienting (Doricchi et al., 2010), which is congruent with our lesion symptom mapping findings (Chapter 3, Chechlacz et al., 2012). Specifically, Doricchi et al. (2010) demonstrated that the left as well as the right TPJ was activated by stimulus driven orienting to the appropriate side of space. Finally, the findings presented in Chapters 2-4 add to the growing body of evidence suggesting that neuropsychological syndromes can result from

disconnections within attentional selection networks. These arguments are presented in following part of this chapter.

Acute vs. chronic neglect: findings, conclusions and limitations

In the last empirical chapter (Chapter 5) I applied voxel-wise lesion symptom mapping approaches to examine differences underlying acute and chronic visuospatial deficits associated with the neglect syndrome following stroke. Similarly to Chapter 2, the last empirical chapter also examined the relationship between two neglect symptoms, allocentric vs. egocentric neglect. This chapter also differed from the others here by using computed tomography scans acquired as part of routine clinical diagnosis to provide the neural basis of the lesion-symptom analysis. This particular chapter went beyond previous reports examining the neural basis of recovery of function by distinguishing different neglect symptoms. This study fits well with potential future research directions concerned with the recovery and rehabilitation of visuospatial disorders (see below). The data presented in Chapter 5 provided evidence that the substrates of persistent neglect symptoms could be predicted based on clinical scans acquired by the time of stroke diagnosis. Furthermore, the results fit well with findings presented in Chapter 2 (Chechlacz et al., 2010) based on analyses using high resolution MRI scans and behavioural data from chronic neuropsychological patents. Specifically, the findings in Chapter 5 indicated that lesions in the angular gyrus were associated with persistent allocentric symptoms, while lesions within the superior temporal gyrus extending into the supramarginal gyrus, as well as within the basal ganglia and insula, were associated with persistent egocentric neglect. In addition to this, a conjunction analysis revealed that damage within the temporo-parietal junction was associated with persistent cancellation errors associated with both types of neglect. Finally, white matter disconnections

resulting from damage within the SLF were associated with both types of neglect (i.e. allocentric as well as egocentric), and critically related to both sub-acute and chronic deficits.

To conclude, the study presented in Chapter 5, together with previous work (Karnath et al., 2011) looking into the neuroanatomy of acute versus chronic egocentric (spatial) neglect, generated important insights into recovery of function, providing the anatomical and methodological basis for further research looking into imaging markers for neglect recovery. The findings presented in Chapter 5 are in agreement with Karnath et al. (2011) who reported a critical role of damage within STG and white matter disconnections in chronic egocentric neglect symptoms. The aim of Chapter 5 was somewhat different from that of Karnath et al. (2011) as it tried to test the suitability of clinical rather than experimental data to predict acute versus chronic symptoms. Furthermore, the findings go beyond these presented by Karnath et al. (2011) by fractionating between different neglect symptoms, which have previously been linked to contrasting recovery profiles (e.g., Bickerton et al., 2011).

Both studies (Chapter 5 and Karnath et al., 2011) provide strong evidence that, although widespread patterns of lesions are associated with neglect at a sub-acute stage, only some lesions are critical for predicting whether neglect will become a chronic disorder. However, these findings might be somewhat affected by the limitations resulting from the neuroimaging techniques. First, both CT and standard MRI scans fail to detect potentially occurring cortical dysfunctions within regions that are structurally intact but have inadequate cortical perfusion. Such regions are likely contributors to cognitive deficits and indeed previous reports link cortical malperfusion to deficits in spatial attention (e.g. Hillis et al., 2005; Hillis et al., 2000; Ticini et al., 2010; Karnath et al., 2005). Interestingly, recent work suggests that reperfusion within cortical regions in acute/subacute phase following stroke can selectively improve different neglect symptoms in the acute phase (Khurshid et al., 2011).

Whether this is also the case for more chronic cases has yet to be assessed. In addition, recovery of function following stroke has been linked to changes in patterns of brain activity as assessed with fMRI (for review see Grefkes and Fink, 2011; Johansen-Berg, 2007a). Indeed previous reports indicate that the brain damage associated with neglect is associated with abnormal activation within intact regions normally involved in spatial attention, while recovery correlates with the normal restoration of activity within these regions and/or compensatory recruitment of functionally related brain areas (Corbetta et al., 2005; He et al., 2007; Thimm et al., 2008). These results indicate that further studies examining neglect recovery are needed to provide a full picture – including tests of the link between white matter disconnections, changes in brain activity patterns and malperfusion within cortical areas, and how these changes relate to functional recovery.

Neuroanatomy of visuospatial attention deficitss – clinical implications

The visuospatial attention syndromes examined in this thesis, unilateral neglect, extinction and simultanagnosia, have significant impact on daily activities of affected individuals and often contribute to poor return to independent living (e.g., Campbell and Oxbury, 1976; Denes et al., 1982; Luaute et al., 2006). These disorders not only have a significant impact on the overall outcome following brain damage but also have proven to be difficult to understand and treat (e.g. Parton et al., 2004; Rizzo and Vecera, 2002; Singh-Curry and Husain, 2010).

Unilateral neglect, extinction and simultanagnosia often co-occur and most notably individual patients frequently present with heterogeneous symptoms associated with a single disorder. Moreover, the extent of visuospatial impairments in individual patients is often exacerbated by deficits in non-spatial cognitive process (Singh-Curry and Husain, 2010).

Subsequently, full information about the nature and extent of neuropsychological symptoms combined with lesion location and understanding the neuroanatomy associated with specific symptoms are key to both evaluating cognitive deficits of individual patients and planning individual patient care and rehabilitation. Thus, the findings presented in the empirical chapters of my thesis are not only critical for understanding the neuroanatomy of visuospatial attention syndromes but this information also carries tangible clinical relevance.

Importantly, while many previous studies have reported neuronal substrates of acute/subacute deficits (e.g. Karmath et al., 2004a; Karnath et al., 2009; Medina et al., 2009; Ticini et al., 2010; Verdon et al., 2010), my work examines neuroanatomy of chronic symptoms (Chapters 2-4; Chechlacz et al., 2010; Chechlacz et al., 2011; Chechlacz et al., 2012). This has direct implication for understanding the nature of persistent symptoms and also indicates the importance of understanding how at the acute/subacute stage brain areas that might be structurally intact but temporarily malfunctioning and at the chronic stage areas affected by plastic reorganizations contribute to patients' potential of rehabilitation. To date little is known about the mechanisms underlying spontaneous recovery and the factors contributing to favourable outcome of visuospatial deficits rehabilitation (Kerkhoff, 2001; Singh-Curry and Husain, 2010). As the final empirical chapter (Chapter 5) examines the neuroanatomy of subacute relative to chronic deficits associated with neglect, these findings point towards the possibility of development of clinically useful tools for predicting stroke functional outcomes from clinical CT scans based on either machine learning approaches using pattern recognition methods or classification algorithms using logistic regression models (e.g., Phan et al., 2010; Reid et al., 2010; Saur et al., 2010). Such approaches could be also developed as useful clinical tools applicable in planning strategies for the most effective rehabilitation to ameliorate visuospatial deficits in individual patients. Furthermore, all the

empirical chapters provide strong evidence that white matter disconnections within long association pathways greatly contribute to visuospatial deficits and advocate the importance of thorough assessment of white matter damage as a part of clinical neuroimaging protocols. To conclude, the findings presented in this thesis have implications not only for basic cognitive neuroscience - by furthering our understanding of the neuroanatomy of visuospatial processes – but they also have clinical impact by helping to unveil the nature of cognitive symptoms observed in individual patients and thus have potential to help plan rehabilitation. Furthermore, the results presented in Chapter 5 strongly advocate that the use of clinical CT scans to develop novel tools for making meaningful predictions of clinical outcome following stroke is not only an attractive but also feasible possibility.

WHITE MATTER LESIONS: VISUOSPATIAL DISORDERS AS DISCONNECTION SYNDROMES

The data presented in the empirical chapters of my thesis provide strong and converging evidence linking white matter disconnections to cognitive deficits associated with the visuospatial syndromes of neglect, extinction and simultanagnosia.

Previously there have been arguments that neglect can be viewed as a disconnection syndrome, following a simple idea that neglect symptoms result from structural disruption of connectivity within frontoparietal attention networks (Bartolomeo et al., 2007; Doricchi and Tomaiuolo, 2003). Consistent with this, there is now a growing body of evidence that neglect is associated with damage to the superior longitudinal (SLF; Chechlacz et al., 2010 [see Chapter 2]; He et al., 2007; Thiebaut de Schotten et al., 2008; Karnath et al., 2009), the inferior longitudinal (ILF; Bird et al., 2006; Chechlacz et al., 2010; Riddoch et al., 2010) and the inferior fronto-occipital fasciculi (IFOF; Chechlacz et al., 2010; Riddoch et al., 2010;

Urbanski et al., 2008) i.e. the long association pathways associated with spatial attention, spatial orienting, visual selection and spatial working memory (Aralasmak et al., 2006; Schmahmann and Pandya, 2006; Schmahmann et al., 2007). Whether white matter disconnections may play a role in extinction and simultanagnosia, and whether there are common or separate white matter disconnections in different visuospatial disorders, are question not examined previously. The work presented here demonstrated that common white matter disconnections along the SLF, ILF and IFOF contribute to symptoms associated with not only heterogeneous neglect symptoms but also with extinction. Furthermore, while unilateral damage to long association pathways within the lesioned hemisphere are linked to neglect and extinction (Chapter 2 and 3 [Chechlacz et al., 2010; Chechlacz et al., 2012), bilateral white matter disconnections are associated with poor visual processing of multiple objects and the loss of processing speed in simultanagnosia (Chapter 4, Chechlacz et al., 2011). The potential functional contribution of individual white matter pathways is discussed extensively in the empirical chapters of the thesis. Here I will revisit the concept of the 'disconnection syndrome' and further discuss its applicability to visuospatial disorders.

The concept of a 'disconnection syndrome' can be traced back to the forefathers of cognitive neuropsychology such as Carl Wernicke, Hugo Liepman and Jules Dejerine. However, the popularity of the concept can be credited to the work of Norman Geschwind who presented a revised disconnection account of many neurological disorders (Geschwind, 1965a, b; for review see also Catani and Ffytche, 2005; Catani and Mesulam, 2008). According to the classical disconnection concept as put forward for example by Wernicke, a disconnection syndrome can be viewed as a disorder of higher cognitive function resulting from a breakdown of associative connections between cortical areas due to white matter lesions (Wernicke, 1874). In contrast to this, Geschwind viewed disconnection syndromes as

disorders of higher cognitive functions resulting from either white matter lesions or lesions within association cortices, which serve as relay posts between primary motor, primary sensory and limbic cortical areas (Geschwind, 1965a). Regardless of the specifics of the disconnection concept, it has a very appealing applicability to visuospatial disorders. First, it can be argued that the cognitive processes underlying spatial attention and visual selection are derived from a widely distributed neuronal network subserved by long association fronto-parietal and fronto-occipital white matter pathways (Schmahman and Pandya, 2006; Makris et al., 2005; Petrides and Pandya, 2006). Secondly, many previous reports have demonstrated a strong relationship between white matter lesions and neglect and this thesis has provided converging evidence indicating that such correlations are also significant for extinction and simultanagnosia (see above). The findings were particularly striking and interesting in relation to simultanagnosia (Chapter 4 [Chechlacz et al., 2011]). The initial simple lesion overlap analysis across simultanagnosic patients revealed a widespread overlap of bilateral lesions within white matter areas along with much higher variability in the pattern of grey matter lesions. Subsequently, detailed analysis of the white matter (e.g., using a lesion laterality index and diffusion tractography) indicated that bilateral parieto-occipital white matter disconnections are both distinctive and necessary to create the symptoms associated with simultanagnosia. This may also relate to functional accounts of simultanagnosia, which stress the role of decreased processing speed (Duncan et al., 2003), which might reflect decreased connectivity within the visuospatial attention network. Finally, it is worth noting that in the past there have been many heated debates with regards to the critical lesions associated mainly with neglect and to a lesser extent also with extinction (e.g., Mort et al., 2003 vs. Karnath et al., 2001; see Chapters 2 and 3 for comprehensive review). Although some of these controversies have been addressed by recent studies, which fractionate the heterogeneous

visouspatial symptoms that comprise these disorders (e.g. Verdon et al., 2010; Chechlacz et al., 2010 [Chapter 2]; Medina et al., 2009; also here Chapters 3 and 4 [Chechlacz et al., 2011; Chechlacz et al., 2012), the concept of a disconnection syndrome also provides an elegant and highly plausible solution.

NEUROIMAGING APPROACHES TO STUDYING VISUOSPATIAL ATTENTION: LESION SYMPTOM MAPPING VS. OTHER METHODS

Lesion-symptom mapping of visuospatial attention – methodological remarks

The research presented in this thesis not only provides novel findings but also goes beyond the previous work in terms of applied lesion-symptom mapping methods. The great majority of previous studies examining the neuroanatomy of neglect (e.g. Karnath et al., 2004; Karnath et al., 2009; Bird et al., 2006; Medina et al., 2009; Hillis et al., 2005) have used manual delineations of lesions and reduction approaches to the behavioural data (i.e. categorically dividing patients to those with and without neglect) - procedures that have several limitations (see Chapters 1 and 2 for further discussion). By contrast the results presented in Chapter 2 were obtained based on voxel-based morphometry (VBM; Ashburner and Friston, 2000), analyses using continuous behavioural scores and information from segmented grey and white matter tissue. These methods are non-biased in terms of the selection of the affected brain regions and they also take into account areas of atrophy that can contribute to the functional deficits in patients (Gottesman et al., 2008). Furthermore, such an approach facilitates the analysis of both grey and white matter substrates of cognitive deficit. The approach as used in Chapter 2 also enables the investigator to identify damage to specific white matter tracts by combining VBM analysis based on segmented white matter with analyses based on diffusion data. Finally, VBM was contrasted with VLSM, which uses non-

parametric statistics and provides converging evidence on voxel-wise approaches to lesion-symptom mapping. Subsequently, Chapter 2 presents the first report on the use of voxel-based analyses of segmented grey and white matter as well as on FA maps (derived from DTI) in combination with continuous behavioural scores to decompose the neuroanatomy of different neglect symptoms.

Similarly to Chapter 2 (Chechlacz et al., 2010), and contrasting with previous lesion symptom studies of extinction (e.g. Karnath et al., 2003; Ticini et al., 2010), Chapter 3 (Chechlacz et al., 2012) employed whole brain statistical analyses, VBM, in order to look for common and dissociated structure-function relationships between neglect and extinction across the whole brain. Importantly, all behavioural measurements were treated as continuous variables rather than categorical scores and analyses controlled for potential confounding factors including the aetiology (stroke, degenerative changes), age-related change, time since lesion, lesion volume and visual field deficit. In Chapter 4 (Chechlacz et al., 2011) a direct contrast was made between a traditional lesion overlap/lesion subtraction approach with analyses based on VBM and diffusion tractography, in this case to explore the neuroanatomy of simultanagnosia. The study used just seven simultanagnosia patients, which is larger than any prior analysis in the literature, but nevertheless presents a considerable challenge for the study of brain-behaviour relationships. Due to the limited numbers involved, the study contrasted different lesion-symptom mapping approaches based on both high resolution anatomical MRI and diffusion tensor imaging. Interestingly, the different approaches provided complementary if not fully converging findings and the study highlighted the pro's and con's of traditional lesion overlap/subtraction methods vs. advanced whole brain voxel-wise analysis (VBM) and diffusion tractography.

Taking the results together, the work presented here indicates that advances in understanding lesion-symptom relations come about not simply through application of the newest and most fashionable techniques but through the use of converging methods that complement the limitations present in each, and that depend on the nature of the data at hand.

Anatomy of visuospatial attention – beyond lesion-symptom mapping

Lesion-symptom mapping approaches in neuropsychological patients are not the only methods widely applied to study human visuospatial attention, which has also been studied extensively using functional neuroimaging and TMS in healthy control participants (for review see Corbetta and Shulman, 2002; Chambers and Heinen, 2010; Driver et al., 2010; Ro, 2010). Importantly, the neuropsychological studies provide sometimes divergent and challenging findings to the data from fMRI (e.g. Galati et al., 2000; Doricchi et al., 2010; Shulman et al., 2010), TMS (e.g. Pascual-Leone et al., 1994; Battelli et al., 2009; Hilgetag et al., 2001) and computational modelling studies (e.g. Heinke and Humphreys, 2003; Lanyon and Denham, 2010; Mavritsaki et al., 2010; Mavritsaki et al., 2009). Here I briefly touch on some of the issues for attempts to seek convergence across the different approaches.

For example, the temoro-parietal junction (TPJ) is an important component of the network consisting of frontal and temporo-parietal substrates mediating attention and awareness of salient stimuli (Downar et al., 2002; Mesulam, 1981). The functional roles of TPJ in visuospatial attention have been extensively studied by both fMRI and computational modelling (Corbetta and Shulman, 2002; Doricchi et al., 2010; Downar et al., 2000, 2001, 2002; Mavritsaki et al., 2010; Mavritsaki et al., 2009). The data presented in my thesis provides novel evidence based on lesion symptom mapping that importantly adds to the current understanding of the TPJ function based on existing data from functional imaging and

computational modelling studies. As already discussed (see above) the results presented here are consistent with Mavritsaki et al. (2010) proposal that the TPJ acts as a form of saliency map that promotes shifts of attention to behaviourally relevant items and this fit well with data presented in my thesis demonstrating that damage within right TPJ leads to both neglect and extinction. Secondly, though it has been suggested that the right TPJ may play a more dominant role, the findings here indicate that the left as well as right TPJs are involved respectively with right and left extinction. This in turn suggests that this salience-detection function of the TPJ is bilateral supporting recent findings by Doricchi et al. (2010) indicating the role of both left and right TPJs, rather than right TPJ alone, in attentional orienting. Finally, I have demonstrated here that the involvement of TPJ is not limited to indentifying salient visual stimuli but that the TPJ plays a general role in identifying salient events in the sensory environment across multiple modalities (evidence based on damage within TPJ lined to both visual and tactile exctinction). This important notion is consistent with prior fMRI findings from healthy participants showing the involvement of the TPJ across multiple sensory modalities: visual, tactile and auditory (Corbetta and Shulman, 2002; Downar et al., 2000, 2001, 2002).

Lets consider another example. Many fMRI studies strongly link the intraparietal sulcus (IPS) to spatial attention (e.g. Corbetta et al., 1993; Giesbrecht et al., 2003; Nobre et al., 1997; Vandenberghe et al., 2005). These findings however have been questioned based on prevalent data from neuropsychological patients linking other parietal and temporal areas to spatial attention (e.g. Mort et al., 2003; Karnath et al., 2004; Hillis et al., 2005; Karnath et al., 2003; Bird et al., 2006). Due to these discrepancies two recent neuropsychological studies specifically addressed the role of the IPS in spatially selective attention. The new data and provide strong evidence linking the IPS to selection between competing stimuli (Gillebert et

al., 2011; Molenberghs et al., 2008). For example, Gillebert et al. (2011), based on combined behavioural testing and functional imaging, demonstrate that patients with IPS lesions for contralesional targets have impaired a spatial focus of attention and ability to select between competing stimuli. Data supporting these findings on the role of IPS is also presented in this thesis, where I showed that damage within IPS was linked to neglect and also to simulatanagnosia. Finally, a recent review of neuropsychological evidence from simultanagnosia patients (see Riddoch et al., 2010) strongly indicates the role of the IPS in spatial attention and in particular its link to the selection of low saliency stimuli.

Besides fMRI, transcranial magnetic stimulation (TMS) in healthy controls has been frequently used to study visuospatial attention (for recent review see Driver et al., 2010; Ro, 2010; Chambers and Heinen, 2010). Studies using TMS have demonstrated homolog results on visual extinction to match the findings from neuropsychological patients, but in this case showing a selective deficit in visuospatial selection after stimulation to the posterior parietal cortex (e.g. Battelli et al., 2009; Critchley, 1949; Hilgetag et al., 200; Pascual-Leone et al., 1994; Ress et al., 2000). Reports based on lesion analyses in groups of stroke patients however have provided inconsistent results with visual extinction found after lesions outside the parietal cortex – with critical regions including the dorsolateral frontal cortex (Vallar et al., 1994), visual association cortex (Hillis et al., 2006a), TPJ (Karnath et al., 2003; Ticini et al., 2010) and subcortical (basal ganglia) structures (Ogden, 1985; Ticini et al., 2010; Vallar et al., 1994). Strikingly, the data presented in Chapter 3 examining the neuroanatomy of extinction provide evidence confirming the TMS findings with regards to the posterior parietal cortex as well as reconciling some of the finding from earlier neuropsychological studies, especially with regards to the TPJ and basal ganglia. Thus it can be suggested that lesions to several areas of the visuospatial attentional network can unbalance selection so that

a biases emerges favouring ipsilesional over contralesional stimuli – but the posterior parietal cortex can certainly be counted amongst these regions.

To conclude, the inferences about the functional organization of human cognition can be made based on a variety different approaches. While the development of cognitive neuroscience techniques such as fMRI, TMS and computational modelling challenge the relevance of cognitive neuropsychology and lesion-symptom mapping methods, it can still be argued that lesion-symptom mapping remains an important and indispensable approach. Indeed an important point is that it is not just lesion-symptom mapping that suffers from limitations and difficulties. TMS for example can induce both excitatory and inhibitory changes depending on the protocol, and there may be additional effects in other brain areas (not directly stimulated), which are uncontrolled and poorly understood. In addition, fMRI is based on a correlatory approach and thus does not allow inferences to be made about the necessary role of particular brain areas. Consequently, it remains vital and valuable to be able to draw conclusions based on converging evidence provided by different methods.

DIRECTIONS FOR FUTURE RESEARCH

The visuospatial disorders studied in this thesis have two important things in common, one relating to clinical aspects of the disorders and one to basic scientific implications: (i) the impairments evaluated here severely affect daily functioning, and the persistent symptoms associated with the syndromes are usually difficult to treat; and (ii) the impairments can provide important insights into the cognitive processes underlying spatial attention and visual selection. Future studies are required into both aspects – but most notably, assessments of the mechanisms of recovery and rehabilitation may themselves benefit both basic cognitive neuroscience and clinical practice. I discuss several examples.

As there is a strong link between persistent visuospatial deficits and overall poor functional outcome after stroke, it would be interesting to follow up on the study presented in Chapter 5 and further examine the predictors of spontaneous functional recovery as well as successful rehabilitation. One potential idea would be to combine structural and functional MRI in sub-acute and chronic phases following stroke in relation to the onset of visuospatial deficits. Such an approach would support the examination not only of patterns of lesions and the structural changes linked to different degrees of recovery (as in Chapter 5), while at the same time generating insights into the patterns of brain activation associated with good/poor recovery. For example, is recovery associated with the development of compensatory mechanisms for cueing/attending to the affected (contralesional) side. The link between changes in patterns of brain activity assessed with fMRI and neglect recovery and rehabilitation has been started, but remains in its infancy (e.g. Corbetta et al., 2005; He et al., 2007; Soto et al., 2009; Thimm et al., 2008; see also Johansen-Berg, 2007; Grefkes and Fink, 2011 for reviews on functional imaging of stroke recovery). The idea here would be to go beyond these studies by (for example) simultaneously examining, changes in the pattern of brain activation linked to measures of connectivity based on diffusion imaging within both the affected and the contralesional hemisphere (see previous reports looking into networks reorganizations following stroke e.g. Crofts et al., 2011; Grefkes and Fink, 2011; Grefkes et al., 2008; Sharma et al., 2009; Stinear et al., 2007). Furthermore, it would interesting to examine link between changes in the patterns of brain activation and the time course of malperfusion and reperfusion of cortical areas following onset of visuospatial deficits in relation to the improvement of symptoms in chronic as well as sub-acute cases.

Future research could also potentially explore the use of information gathered in the empirical chapters of this thesis to further our understanding of structural connectivity within

the brain regions supporting visuospatial attention. The specific idea would be to tease apart structural connectivity for visouspatial attention by combining diffusion imaging based probabilistic tractography in a group of healthy controls with VBM results from a group of neuropsychological patients. Specifically, it would be possible to use as seed points clusters previously identified by VBM as being associated with different aspects of spatial attention (e.g., from the data here), to direct tractography analyses. In this way it may be possible to map the pathways between key regions involved in different processes underlying visuospatial attention.

A final, very different avenue for future research would be to combine TMS and brain imaging method to temporarily mimic brain lesions with functional neuroimaging (fMRI) in healthy controls, to addressed some of the questions unanswered in the thesis. Although the secondary changes in brain activity induced by TMS are not fully understood, the ability of this technique to evoke reversible “lesions” is well documented (for a review in relation to visual attention, see Chambers and Heinen, 2010; Ro, 2010). One main advantage of using TMS in healthy controls over research carried out in patients is that it can better control the pattern of brain lesion (e.g., being less dependent on the vascular territory affected by stroke). Since TMS may create relatively discrete “lesions” which can differentiate between close anatomical areas identified in the present VBM analyses (e.g., the angular and suprmarginal gyri; Chambers et al., 2004; Rushworth et al., 2001), it enables the specific functions of these regions to be isolated. In addition, the application of TMS to normal participants may overcome some of the limitations of using brain lesioned patients, who may for example find it difficult to perform more challenging tasks but for non-critical reasons (e.g., poor verbal comprehension). When combined with fMRI, TMS can also provide data on the necessary role of a given brain area in driving other, connecting regions. One potential area where

combined fMRI/TMS approach would be desirable is for study testing which specific brain regions are involved in balancing the visuospatial resources involved in attending to the left and right parts of objects and in selecting distinct, simultaneously presented objects, particularly as the present results show overlap between the neuronal substrates of extinction and of allocentric neglect (e.g., angular gyrus) – but which are inconsistent with other reports indicating the middle temporal gyrus as critical for encoding the left and right sides of individual objects irrespective of their position in the visual field (Committeri et al., 2004; Khurshid et al., 2011).

CONCLUSIONS

In this thesis I have presented a series of studies, which aimed to decompose the neuroanatomy of different neuropsychological disorders of spatial attention. The experiments have a consistent approach in which they examine (1) neural substrates underlying different neglect symptoms, allocentric versus egocentric neglect, (2) the lesion patterns associated with visual and tactile extinction vs. those related to visual field defects and neglect, and (3) the lesion pattern linked to simultanagnosia, extracting out lesions associated with unilateral visuospatial deficits.

These studies demonstrated that the distinct patterns of grey matter lesions in individual patients, and the laterality of white matter disconnections, determine the degree to which visual processing and spatial attention are disrupted and thus the nature of the observed cognitive symptoms. I have argued that these findings not only provide insights into the neuroanatomical organization of the brain but also the functional organization of the neuronal network supporting visuospatial awareness. The data have strong implications for functional accounts of the syndromes. In particular I argued that (1) my findings support the dissociation between allocentric and egocentric neglect and suggest that they respectively reflect problems

in ‘between’ and ‘within object’ spatial representations. The finding of distinct neuroanatomical correlates for the disorders disputes Driver and Pouget (2000) proposal that both forms of neglect stem from a gradient of attention across egocentric space; (2) visual extinction and allocentric neglect are potentially functionally related. Here the data suggest specifically that a failure to balance processing resources when the left and right sides of an object or region of space are being processed may together lead to both impairments (extinction and allocentric neglect) and (3) at a functional level, the bilateral white matter disconnections in simultanagnosia are consistent with Duncan et al.’s (2003) argument linking this syndrome to severe impairments in visual processing speed. Overall, the findings presented support a ‘disconnection syndrome’ account of the different visuospatial disorders. Finally, the last study, examining the neuroanatomy of acute relative to chronic neglect symptoms, not only provided further evidence for the functional distinction between allocentric and egocentric neglect (see above) while also demonstrating that persistent neglect symptoms can be predicted from computed tomography scans acquired as a part of clinical diagnosis.

Throughout the thesis I have discussed and contrasted the pro’s and con’s of different approaches to lesion-symptom mapping with regards to the theoretical implications for understanding the nature of human visual attention. Contrasting the presented data with the findings from functional neuroimaging, TMS and computational modelling, I conclude here that a cognitive neuropsychological approach based on modern lesion-symptom mapping methods is far from being a relict of past research era but has the potential to provide important insights into our understanding of human cognition.

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APPENDIX 1:

SUPPLEMENTARY MATERIAL – CHAPTER 2

Supplementary Table 1. Patients details: clinical and demographic data

ID	Sex/Age/ Handedness	Aetiology	Time post lesion	Lesion side	VFD	Apple Cancellation Score(/50)***	Asymmetry Score: Full Apples***	Asymmetry Score: Incomplete Apples***	Apple test/re-test	Non-word reading
P1	M/55/R	S	4	B	_	46	2	0	0 (0)	0 (0)
P2	M/60/R	S	12	R	_	47	0	0	0 (0)	0 (0)
P3	F/81/R	S	10	R	_	50	0	0	0 (0)	0 (0)
P4	M/63/R	S	5	B	_	**22**	**22**	**2**	1 (1)	1 (1)
P5	F/65/R	CBD	4	B	_	**10**	**10**	**3**	1 (1)	1 (1)
P6	M/71/R	S	14	L	_	50	0	0	0 (0)	0 (0)
P7*	M/38/R	CM	12	R	_	49	0	0	0 (0)	0 (0)
P8*	M/70/R	CM	12	B	_	50	0	0	0 (0)	0 (0)
P9	M/52/R	HSE**	15	R	_	50	0	0	0 (0)	0 (0)
P10	M/66/R	S	18	B	+ (L)	**14**	**14**	**4**	1 (1)	1 (1)
P11	M/85/R	S	26	B	_	50	0	0	0 (0)	0 (0)
P12	F/63/L	S	3	R	+ (R)	45	3	0	0 (1)	0 (1)
P13	F/72/R	S	4	B	_	50	0	**4**	0 (1)	0 (1)
P14	F/57/R	S	2	L	_	**35**	0	0	1 (0)	1 (0)
P15	M/62/R	CBD	3	R	_	50	0	0	0 (0)	0 (0)
P16	M/61/R	S	5	R	_	50	0	0	0 (0)	0 (0)
P17	M/76/R	S	3	R	_	50	0	1	0 (0)	0 (0)
P18	M/69/R	S	4	R	_	**32**	**18**	**3**	1 (1)	1 (1)
P19	F/60/R	S	1	R	_	44	3	0	0 (0)	0 (0)
P20	M/65/R	S	2	R	_	**32**	**9**	1	NT	NT
P21	M/64/R	S	1	R	_	**40**	**10**	**4**	1 (1)	1 (1)
P22*	M/54/L	CM	10	L	_	50	0	**-4**	0 (1)	0 (0)
P23	F/81/R	S	1	L	_	**32**	**-18**	-1	NT	NT
P24	M/61/L	S	12	R	+ (L)	**40**	**9**	1	1 (1)	1 (1)
P25	M/48/R	S	5	R	_	50	0	0	NT	0 (0)
P26	M/75/R	S	3	L	+ (R)	**36**	0	0	1 (0)	1 (0)
P27	M/32/R	S	1	L	_	49	1	0	NT	NT
P28	M/32/R	S	2	R	_	49	1	0	NT	NT

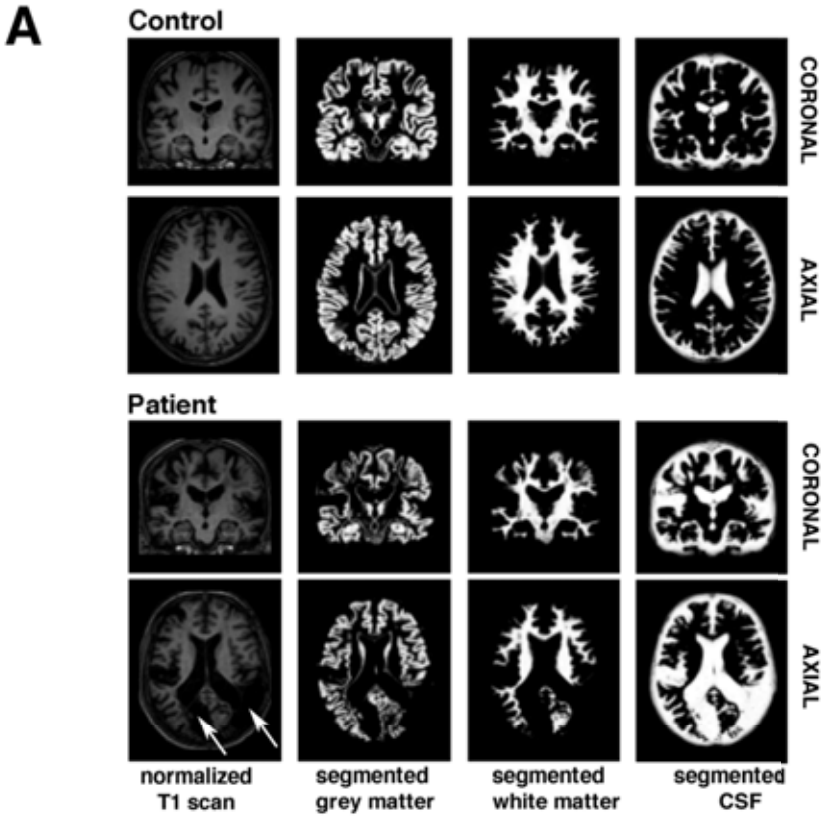
P29	F/60/R	S	13	B	_	47	1	**7**	0 (1)	0 (1)
P30	M/34/R	S	9	L	_	50	0	0	0 (0)	NT
P31	M/72/R	S	4	L	_	50	0	0	0 (0)	NT
P32	M/72/R	S	7	R	_	50	0	0	0 (0)	0 (0)
P33	M/63/R	CBD**	3	B	_	**18**	**-18**	**5**	1 (1)	1 (1)
P34	M/53/R	S	3	R	_	47	3	**9**	1 (1)	1 (1)
P35	M/73/R	S	8	R	_	50	0	**-8**	0 (1)	0 (1)
P36	M/64/L	S	1	R	_	47	3	**2**	0 (0)	0 (0)
P37	M/73/L	S	8	L	_	44	**4**	1	0 (0)	0 (0)
P38	F/58/R	S	4	B	_	50	0	0	0 (0)	0 (0)
P39	M/55/R	HSE**	10	B	_	50	0	0	0 (0)	0 (0)
P40	M/70/R	S	7	R	_	**38**	**12**	**4**	1 (1)	1 (1)
P41	F/78/R	S	1	R	_	**36**	0	0	0 (0)	0 (0)

B = bilateral; CBD = cortico-basal degeneration; CM = carbon monoxide poisoning; HSE = herpes simplex encephalitis; L = left; R= right; S = stroke; VFD = visual field deficits; * 3 patients with CM poisoning who were excluded from the final analysis; ** patients with chronic degenerative changes who were presented with additional acquired brain lesions resulting from unspecified vascular disease; *** The maximum achievable score in the Apple Cancellation task is 50. Egocentric neglect is determined by whether patients miss targets (complete apples) on the left or right side of the page. Allocentric neglect is determined by whether patients make false positive responses by cancelling incomplete apples (distractors) where the gap is on either the right or left side of each apple, irrespective of the position of the (incomplete) apple on the page. Cut-offs to classify patients as having egocentric or allocentric neglect were calculated on the basis of asymmetry scores (left vs. right-side egocentric or allocentric errors), using scores from 86 elderly control participants and were as follows: Egocentric asymmetry for full apples (based on <2.5th percentile) <-2 right side errors or >3 left side errors; allocentric asymmetry for incomplete apples (based on <2.5th percentile) <-1 right side errors or >1 left side errors. The cut-off for total numbers of target omissions i.e. accuracy score was 40/50 (based on <2.5th percentile). Scores where there is a clinical deficit are highlighted in bold. On the Apple test/re-test score we note whether a patient had a clinical deficit when re-tested for egocentric (allocentric, in brackets) neglect. 1= a clinical deficit, 0 = within test norms. The nonword reading test required patients top read aloud 40 randomly positioned pronounceable nonwords on an A4 sheet. A clinical deficit of egocentric neglect was based on 2.5th percentile cut-off on data from 20 elderly control participants (ages 60-75). Egocentric neglect was classified as omitting 2 more nonwords on one side of the page than on the other. Allocentric neglect was classified as making, across the nonwords attempted, 2 more errors at one end of the strings than at the other. 1 = a clinical deficit, 0 = no deficit for egocentric (and allocentric, in brackets) neglect. For the measure of egocentric neglect from the Apples test there was 89% concordance between the classification derived from the test/re-test scores, and an 89% concordance also for the egocentric neglect measures from the Apples test and the nonword reading test. For the measure of allocentric neglect from the Apples test there was 94% concordance between the classification achieved from test/re-test scores and also 94% concordance between the Apples test score and the measure of allocentric neglect in the nonword reading task.

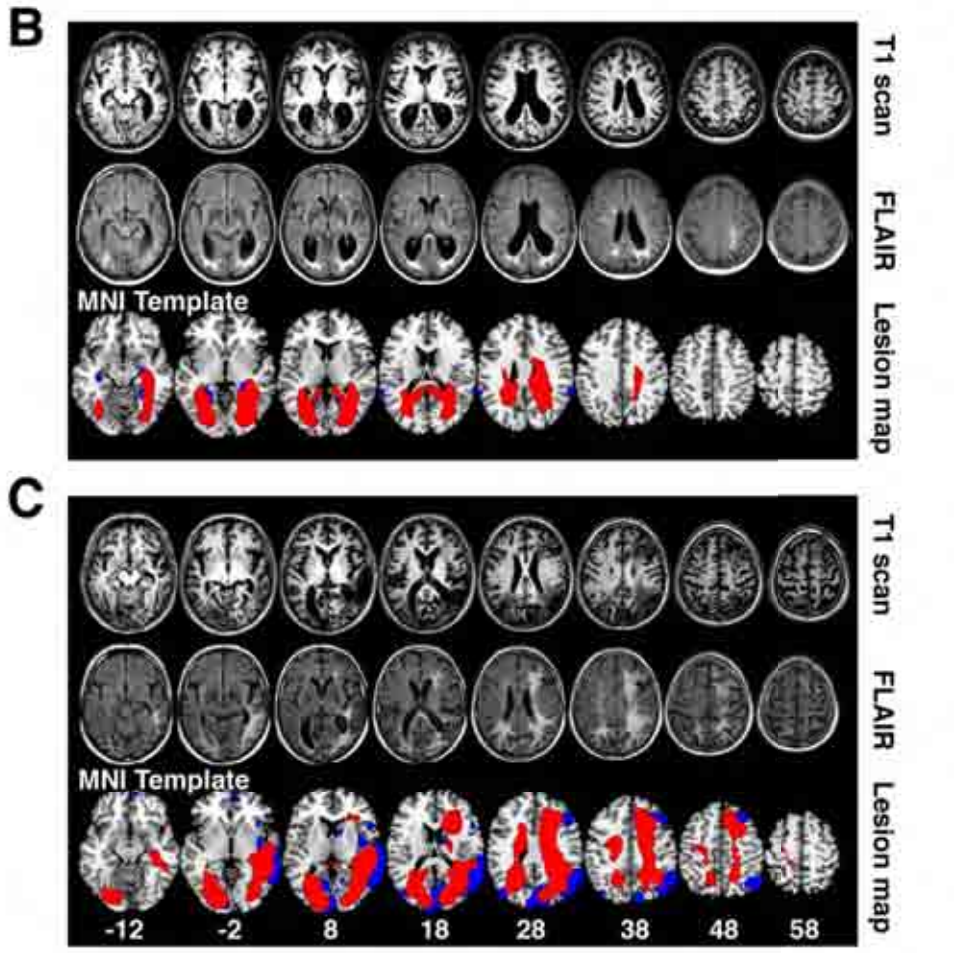
Supplementary Table 2. Normalised behavioural scores

ID	Left allocentric neglect score*	Right allocentric neglect score*	Left egocentric neglect score*	Right egocentric neglect score*
P1	0	0	0	0
P2	0	0	0	0
P3	0	0	0	0
P4	2	0	0.8	0
P5	3	0	0.25	0
P6	0	0	0	0
P7	0	0	0	0
P8	0	0	0	0
P9	0	0	0	0
P10	4	0	0.4	0
P11	0	0	0	0
P12	0	0	0	0
P13	4	0	0	0
P14	0	0	0	0
P15	0	0	0	0
P16	0	0	0	0
P17	0	0	0	0
P18	3	0	1	0
P19	0	0	0	0
P20	0	0	0.5	0
P21	4	0	1	0
P22	0	4	0	0
P23	0	0	0	1
P24	0	0	0.9	0
P25	0	0	0	0
P26	0	0	0	0
P27	0	0	0	0
P28	0	0	0	0
P29	7	0	0	0
P30	0	0	0	0
P31	0	0	0	0
P32	0	0	0	0
P33	5	0	0	0.6
P34	9	0	0	0
P35	0	8	0	0
P36	2	0	0	0
P37	0	0	0	0
P38	0	0	0	0
P39	0	0	0	0
P40	4	0	1	0
P41	0	0	0	0

Supplementary Table 2: *The behavioural scores used as covariates in all voxel-wise neuroimaging analyses were classified based on cut offs drawn from the BUCS (see Methods section for full information). In addition, to account for variation in overall performance affected by general motor and attentional deficits we divided the asymmetry score for full apples by the total number of full apples missed and these scores were used respectively as left and right egocentric neglect covariates.



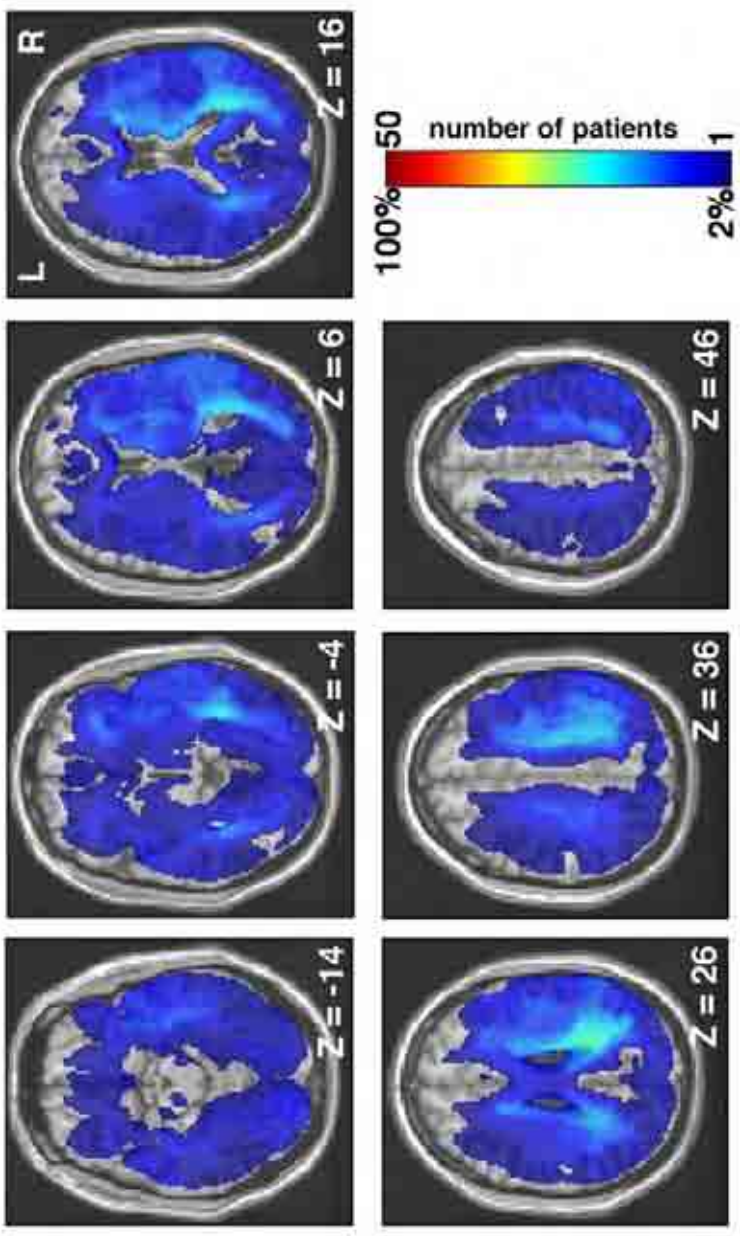
Supplementary Figure 1. Example of the advanced segment-normalize procedure and lesion reconstruction.
(A) Illustration of the output of the advanced segment-normalize procedure applied to high resolution T1-weighted MRI scans from one of the healthy control participants (67 years old male) and one of the neglect patients (63 years old male with left egocentric neglect and left allocentric neglect). This procedure (see Methods for full details) involves tissue classification based on the signal intensity in each voxel and on a-priori knowledge of the expected localization of grey matter, white matter and cerebrospinal fluid (CSF). The outputs of this procedure are 3 classified tissue maps representing the probability that a given voxel 'belongs' to a specific tissue class. The brain tissue affected by stroke (white arrows) is typically mapped with reduced likelihood of representing either grey or white matter due to the change in signal intensities caused by stroke. In the current study we tested only chronic patients and thus in majority of cases the region of the damaged tissue was 'replaced'/ 'filled' by CSF as shown here.



Supplementary Figure 1. (**B**, **C**) Illustration of the reconstructed lesion maps and corresponding T1 and FLAIR scans from two of the neglect patients with degenerative changes (**B:** 65 years old female with left egocentric neglect and left allocentric neglect; **C:** 63 years old male with right egocentric neglect and left allocentric neglect). The bottom row shows binary map of grey (displayed in blue) and white (displayed in red) matter lesions. The binary lesion map is presented as an overlay on a standard T1 multi-slice template in MRIcron (Chris Rorden, University of South Carolina, Columbia SC, USA). MNI z-coordinates of the axial sections are given. For all patients reconstructed lesion maps were verified against the high resolution T1 scans (where available, we also used T2 or FLAIR contrasts, in particular in the case of patients with degenerative changes as shown here) and these lesion maps were further used in VLSM analysis (voxel-based lesion symptom; see Methods for full details). All images in (**A**), (**B**) and (**C**) are displayed in neurological convention i.e. left of the slice represents the left hemisphere.

APPENDIX 2:

SUPPLEMENTARY MATERIAL – CHAPTER 3



Supplementary Figure 2. Lesion distribution
Lesion overlap map representing the spatial distribution of lesions in 50 patients included in the study. Lesion maps from individual patients were reconstructed based on method described by Seghier et al., 2008 (see Chapter 3 Methods section for details). The lesion overlap map is shown for seven axial slices in standard MNI space. The colour bar shows the number and percentage of patients with a lesion within particular voxel (range 1-50 and 2-100%). MNI Z-coordinates of the axial sections are given.

APPENDIX 3:

SUPPLEMENTARY MATERIAL – CHAPTER 4

SUPPLEMENTARY METHODS

Visual extinction

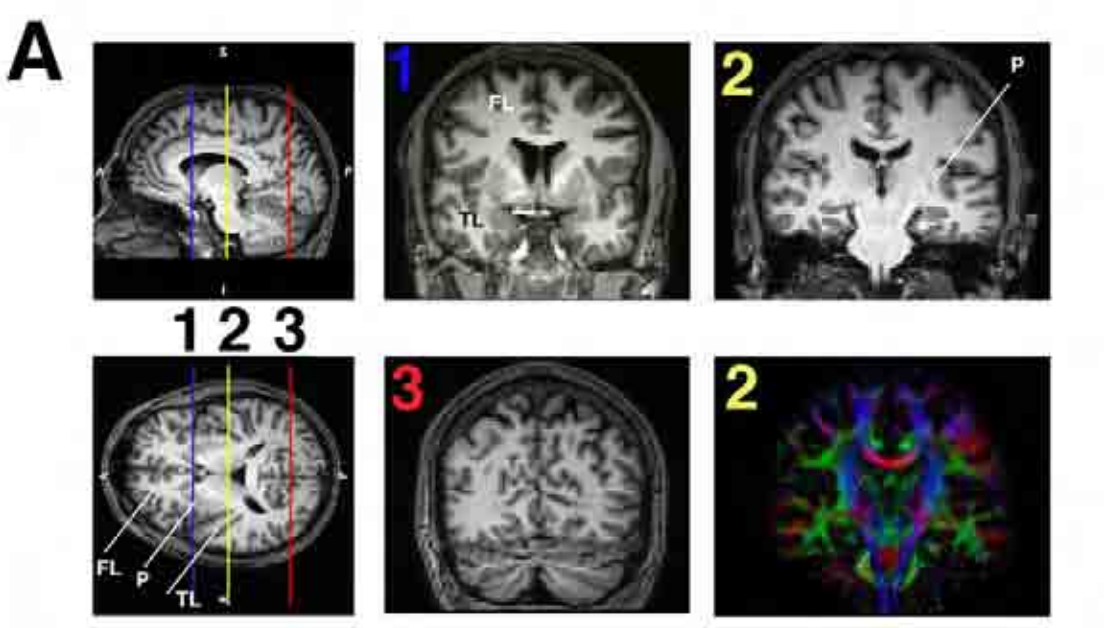
In order to measure visual extinction we used a simple computer test presented on a PC running E-Prime software (Psychology Software Tools). The test was based on a single experimental block consisting of 96 randomized trials. There were 48 single item trials (24 left and 24 right) and 48 bilateral trials. In both unilateral and bilateral trials the stimuli were presented on the black background inside white outlines of rectangles positioned in the left and right hemifield. On unilateral trials patients were presented with stimulus consisting of a single white letter (~0.5deg horizontally and vertically) at the centre of either the left or right rectangle (centred 3deg into each field). On bilateral trials two white letters were positioned respectively at the centre of the left and right rectangles. There were 4 possible targets to identify (the letters A, B, C and D). At the beginning of the test participants were instructed "Your task is to fixate on the centre of the screen and to respond to the appearance of the letter(s) by saying the letter(s) you see out loud". Participants were instructed that they might see more than one letter on a given trial. Each trial began with a 200ms presentation of a white fixation cross on the black background at the centre of screen between the white rectangles. This was followed by brief presentation of a unilateral or bilateral stimulus for 200ms after which patients were asked to freely report the letter(s). The maximum achievable score on bilateral trials was 48 and also 48 (24 left plus 24 right) on unilateral trials. We recoded the number of correct bilateral responses as well as number of right and left omissions (errors) on unilateral and bilateral trials. Based on left and right omissions we calculated an asymmetry score on the difference in report on left- and right-side items, separately for unilateral and bilateral trials. The performance on unilateral trials gives a measure of a field defect or neglect (unilateral bias). Control norms for visual extinction

test were assessed based on performance of 10 control participants with no history of neurological diseases and no lesions on MRI scans (5 males and 5 females, age range 62-74). Cut-offs to classify patients as having visual extinction were calculated on the basis of bilateral asymmetry scores (left vs. right-side errors). Control participants made a maximum of two errors on a single side or both sides and therefore the asymmetry scores >2 were classified as abnormal.

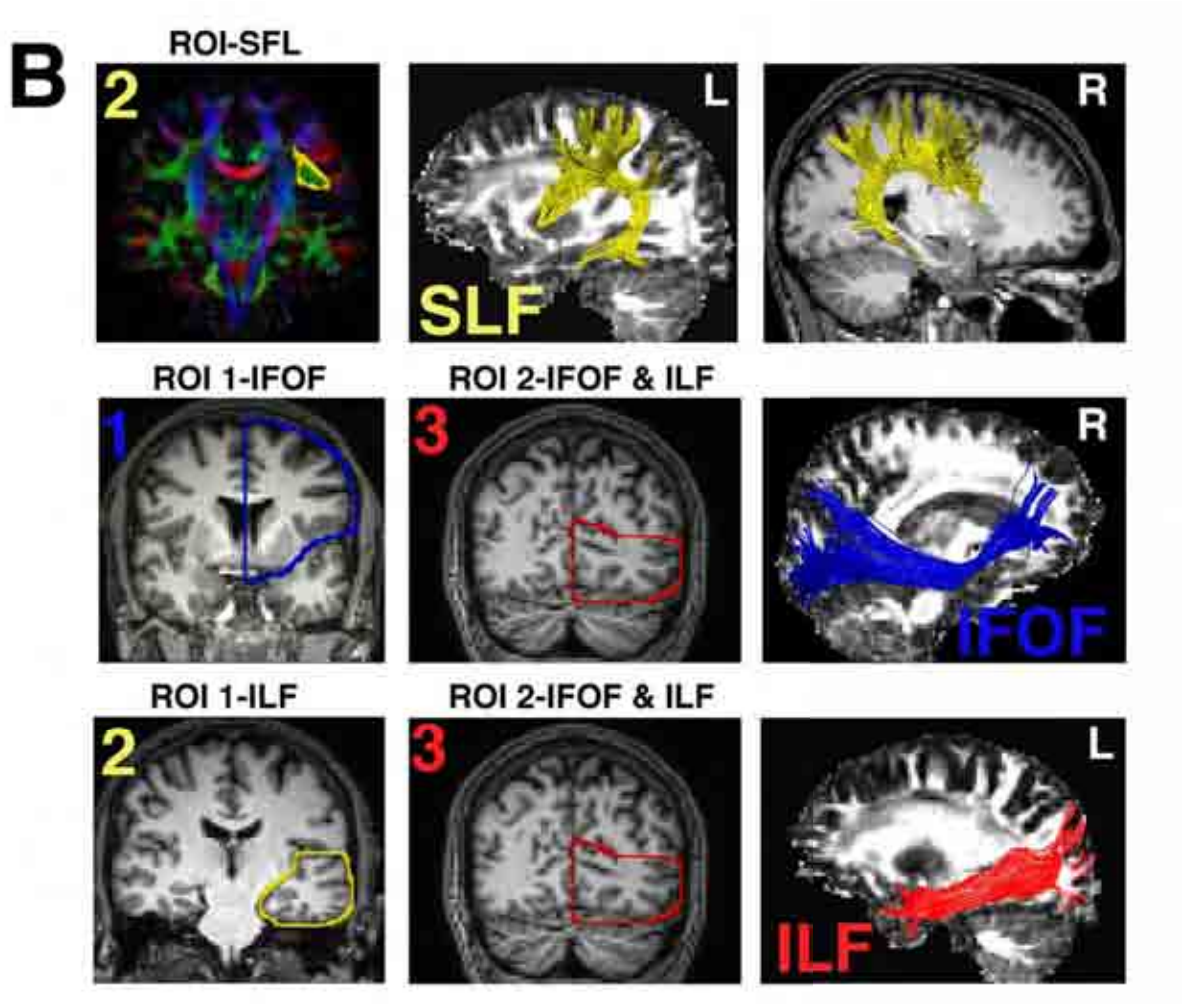
DTI Tractography

Both fibre tracking and tract extractions were performed in native diffusion space. The fibre tracking was first performed from every voxel in the brain and then followed by tract extraction using ROI filters. We applied ROI approach as previously described by Mori et al. (2002) as this method uses large ROI filters and thus is robust and easily replicable for patients with extensive lesions. For consistency, all tracts were extracted using systematic protocols illustrated in Supplementary Figure 1. In order to precisely delineate ROIs on the standard anatomical scans and to compare tracking results with lesion location, the T1-weigthed images for all participants were first re-aligned with b0 volumes and FA maps (output from Diffusion toolkit) and then co-registered and re-sliced using Matlab 7.5 (The MathWorks, Natick, MA, USA) and SPM5 (Welcome Department of Cognitive Neurology, London UK). The locations of the ROIs were determined using either colour-coded FA map or T1 scans of each participant based on anatomical landmarks. First three coronal slices were identified (Supp. Fig. 3a) on T1 scan: slice 1 at the level where the frontal and temporal lobes are separated within left and right hemisphere, slice 2 at the level of the posterior tip of the putamen and slice 3 at the level of parieto-occipital fissure. Next, ROIs were delineated on identified slices. For the superior longitudinal fasciculus (SLF) connecting the frontal, parietal and temporal lobes a single ROI

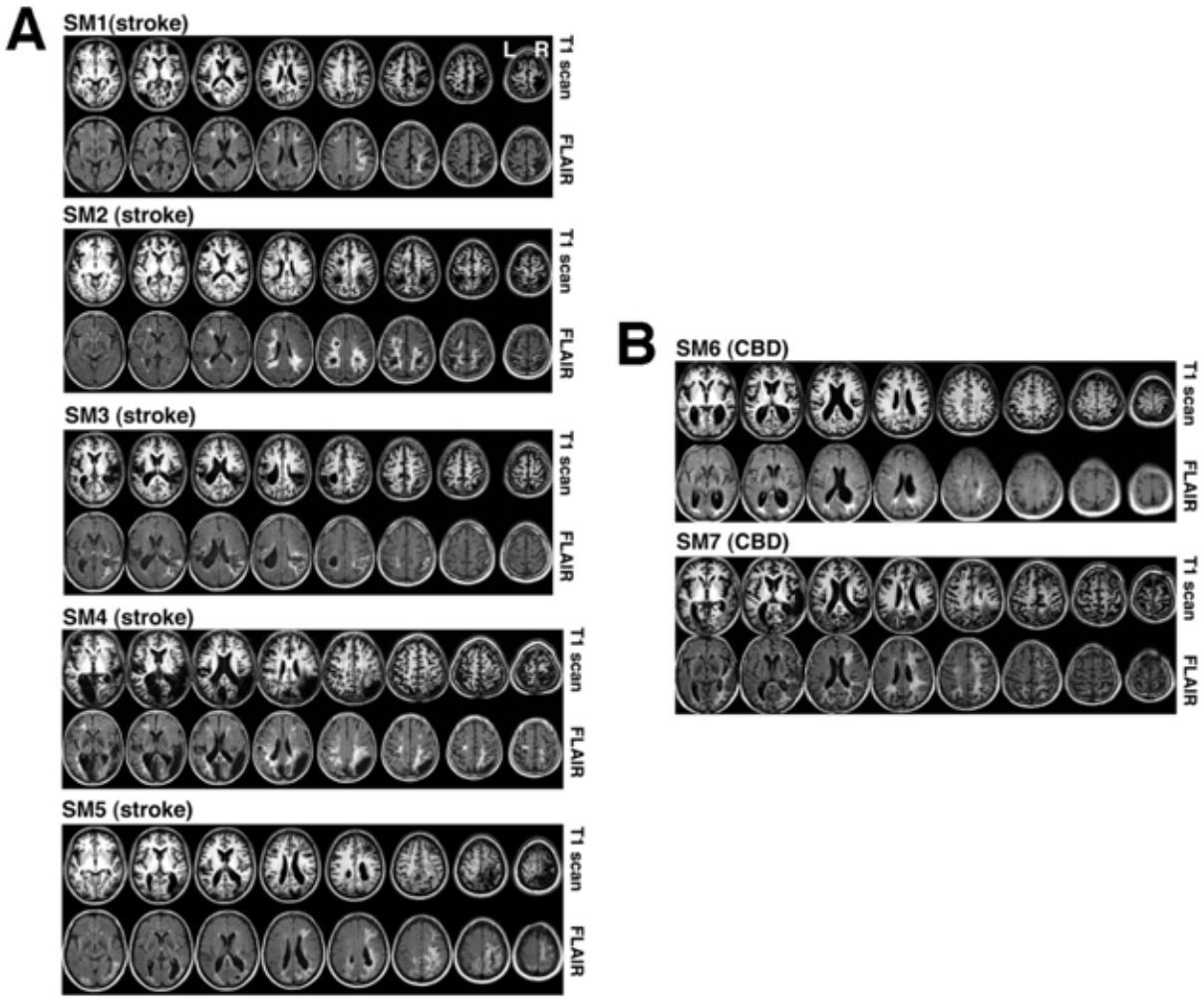
was delineated for each hemisphere on slice 2 using colour-coded FA map as shown in Supp. Fig. 3b (top panel). For the inferior fronto-occipital fasciculus (IFOF) connecting the frontal and occipital lobes, two ROIs were used for each hemisphere: ROI 1 was defined as the frontal cortex on slice 1 and ROI 2 was defined as the occipital cortex on slice 3 (both ROIs were delineated on T1 scan as shown in Supp. Fig. 3b, middle panel). For the inferior longitudinal fasciculus (ILF) connecting the temporal and occipital lobes, two ROIs were used for each hemisphere: ROI 1 was defined as the mid-temporal cortex on slice 2 and ROI 2 was defined as the occipital cortex on slice 3 (both ROIs were delineated on T1 scan as shown in Supp. Fig. 3b, bottom panel). As ILF and IFOF share similar trajectories a two ROI approach as used for the ILF might define both tracts, therefore we also used NO PART operation to exclude IFOF when extracting the ILF.



Supplementary Figure 3. Illustration of the protocol and ROI used for tract extractions
Illustration of the protocol and ROIs used for the extraction of the SLF, IFOF and ILF (see Supplementary Methods for full details). **(A)** Definition of three slices and landmarks used for ROIs delineation: slice 1 (blue) used for ROI 1-IFOF, slice 2 (yellow, both T1 scan and corresponding slice on a colour-coded FA map) used for ROI-SLF and ROI 1-ILF and slice 3 (red) used for ROI 2-IFOF&ILF.



Supplementary Figure 3. (B) The delineation of ROIs for SLF (top panel), IFOF (middle panel) and ILF (bottom panel) plus examples of extracted tracts: SLF (yellow) displayed on FA map (left hemisphere) and T1 scan (right hemisphere) in parasagittal view; IFOF (blue, right hemisphere) displayed on an FA map in parasagittal view; ILF (red, left hemisphere) displayed on an FA map in parasagittal view.
FL, frontal lobe; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; P, putamen; SLF, superior longitudinal fasciculus; TL, temporal lobe.



Supplementary Figure 4. Brain scans – simultanagnosia patients.
T1 and FLAIR scans from seven simultanagnosia (SM1-SM7) patients included in the current study. Patients SM1-SM5 were diagnosed with simultanagnosia resulting from stroke. Patients SM6 and SM7 were diagnosed with simultanagnosia resulting from corticobasal degeneration (CBD; in patient SM7 degenerative changes were presented with additional acquired brain lesions resulting from unspecified vascular disease). All images are displayed in neurological convention i.e. left of the slice represents the left hemisphere. L, left; R, right.

APPENDIX 4:

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(RIDDOCH ET AL., 2010)

Riddoch MJ, Chechlacz M, Mevorach C, Mavritsaki E, Allen HA, Humphreys GW (2010). The neural mechanisms of visual selection: The view from neuropsychology. *Ann.N.Y.Acad.Sci.* 1191: 156-81