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The spatial distribution of perseverations in neglect patients during a nonverbal fluency task depends on the integrity of the right putamen

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ABSTRACT

Deficient inhibitory control leading to perseverative behaviour is often observed in neglect patients. Previous studies investigating the relationship between response inhibition and visual attention have reported contradictory results: some studies found a linear relationship between neglect severity and perseverative behaviour whereas others could not replicate this result. The aim of the present study was to shed further light on the interplay between visual attention and response inhibition in neglect, and to investigate the neural underpinnings of this interplay. We propose the use of the Five-Point Test, a test commonly used to asses nonverbal fluency, as a novel approach in the context of neglect. In the Five-Point Test, participants are required to generate as many different designs as possible, by connecting dots within forty rectangles. We hypothesised that, because of its clear definition of perseverative errors, the Five-Point Test would accurately assess both visual attention as well as perseverative behaviour. We assessed 46 neglect patients with right-hemispheric stroke, and performed voxel-based lesion-symptom mapping (VLSM) to identify neural substrates of perseverative behaviour as well as the spatial distribution of perseverations. Our results showed that the Five-Point Test can reliably measure neglect and perseverative behaviour. We did not find any significant relationship between neglect severity and the frequency of perseverations. However, within the subgroup of neglect patients who displayed perseverative behaviour, the spatial distribution of perseverations significantly depended on the integrity of the right putamen. We discuss the putative role of the putamen as a potential subcortical hub to modulate the complex integration between visual attention and response inhibition processes.

1. Introduction

Visual attention and response inhibition are strongly interrelated in everyday behaviour. The former is crucial for the monitoring of environmental signals (Bari and Robbins, 2013) and the detection of relevant changes. Response inhibition, on the other hand, allows to flexibly adjust behaviour in response to these changes (Bari and Robbins, 2013; van Belle et al., 2014). At the cortical level, a current model suggests that visual attention is controlled by a ventral attention network - which includes the inferior parietal lobule (IPL), the superior temporal gyrus (STG), and the inferior frontal gyrus (IFG) - and by a dorsal attention network, including the medial intraparietal sulcus (mIPS), the superior parietal lobule (SPL), the precuneus, the supplementary eye field (SEF), and the frontal eye field (FEF) (Corbetta and Shulman, 2002; Karnath and Rorden, 2012). The distinct ventral and dorsal attention networks have collaborative roles, allowing flexible adjustment of their dynamic interaction (Vossel et al., 2014). Response inhibition, on the other hand, is controlled by a cortical network including the inferior frontal gyrus (IFG), the dorsolateral prefrontal cortex (DLPFC), the cingulate cortex, and the premotor cortex (Gandola et al., 2013; Husain and Kennard, 1997; Mannan et al., 2005; Menon et al., 2001; Pierrot-Deseilligny et al., 1991). Despite the extensive literature concerning visual attention and response inhibition, theories about these two cognitive functions have mostly been developed separately. Even less is known about how both functions interact, i.e., how visual attention influences response inhibition. One approach to analyse this topic is to assess the behaviour of patients suffering from an impairment of these cognitive functions due to stroke. A lesion

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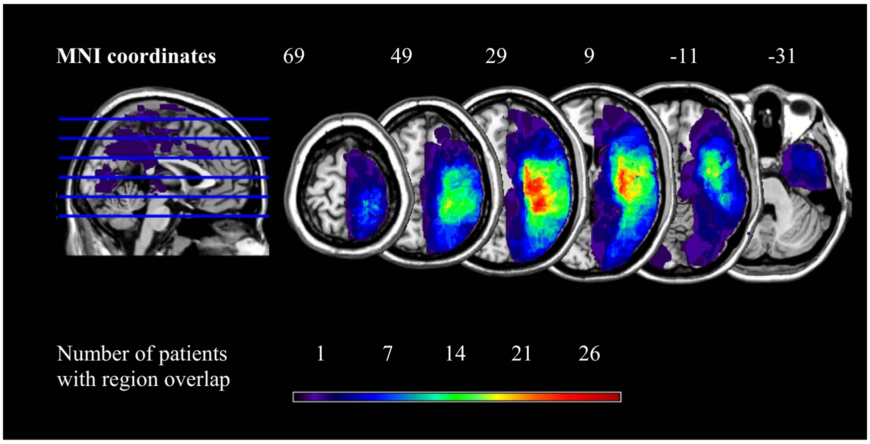

Fig. 1. Brain lesions of all 46 patients with right-hemisphere stroke. The color-coded legend is determined by the number of patients with damage to a specific brain region. Lesion overlap maps are plotted on the CH2 template available in MRIcron (http://www.mccauslandcenter.sc.edu/crnl/tools). Axial slices are oriented according to the neurological convention. The z-position of each axial slice, in MNI coordinates, is indicated by the numbers at the top of the figure, and also depicted by the blue lines on the sagittal slice (left-hand side of the figure). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

involving the attentional network may lead to neglect (i.e., the failure to attend to the contralesional hemispace), whereas another lesion involving the response inhibition network may lead to perseverative behaviour, defined as a failure to inhibit prepotent responses and/or their extension to different behaviours (Jahanshahi et al., 2015; Pia et al., 2009). However, strokes do not follow functional anatomy, but vascularisation, so that especially after extensive strokes (e.g. large MCA strokes) both networks may be damaged at the same time. Indeed, in stroke patients with neglect, perseverations are frequently observed, occurring in 30% (Na et al., 1999) to 90% (Rusconi et al., 2002; Vallar et al., 2006) of cases.

According to Rusconi et al. (2002) and Vallar et al. (2006), neglect and perseverative behaviour can co-occur, but represent two independent disorders, both functionally and anatomically. For instance, in cancellation tasks - where perseverative behaviour in neglect patients can take the form of erroneous re-cancellations of ipsilesional targets or distractors;(Mark et al. (1988), Vallar et al. (2006))- double dissociations between contralesional omissions and perseverative errors have been documented (i.e., some patients show contralesional omissions, but no perseverations, and other patients show the reverse behavioural pattern; Na et al., 1999; Nys et al., 2006; Pia et al., 2009; Ronchi et al., 2009; Rusconi et al., 2002). Moreover, some studies have shown that the number of perseverative errors does not seem to correlate with neglect severity (Pia et al., 2009, 2013; Rusconi et al., 2002; Vallar et al., 2006). However, it has also been shown that visual attention impairment critically influences the number of perseverations. For instance, several studies in patients with neglect demonstrated that perseveration severity is related to neglect severity, and that the amount of perseverative responses linearly increases towards the ipsilesional side of space (Mannan et al., 2005; Na et al., 1999; Nys et al., 2006). Others, in turn, have suggested that the highest degree of perseveration is found in patients with mild to moderate neglect severity, the interaction between neglect and perseveration following an “inverted U-curve” (Kleinman et al., 2013).

The discrepancy between the aforementioned results might be explained, at least in part, by the heterogeneous assessment methods and analysis techniques applied in the different studies. For instance, in cancellation tasks, the assessment of the absolute number of perseverations might lead to biased results, since neglect patients often do not cancel any targets at all within the left, contralesional side of space (e.g. Rusconi et al., 2002). Furthermore, no univocal definition of perseverative errors has been used in previous studies using cancellation tasks (for an overview, see Gandola et al., 2013), leading to very different forms of drawing behaviour being considered as perseverative (i.e., "scribbling" outside of a target, drawing additional targets, drawing cartoons, etc.).

The aim of the present study is to shed further light on the interplay between visual attention and response inhibition in neglect patients, by using a novel assessment that has the potential to measure the spatial deployment of visual attention and perseverative behaviour more accurately. To this end, we used the Five-Point Test (Regard et al., 1982), a sensitive neuropsychological measure of figural fluency, in which perseverative errors are clearly defined. Participants are given three minutes time to generate as many different designs as possible by connecting at least two out of five dots with straight lines. Repeated designs are regarded as perseverative errors. We hypothesised that this test would represent a sensitive instrument to assess both spatial biases in visual attention and perseverative behaviour in neglect patients. Moreover, we aimed at investigating the neural correlates subtending the interaction between visual attention and response inhibition, using voxel-based lesion-symptom mapping (VLSM).

2. Methods

2.1. Subjects

Forty-six patients suffering from left-sided visual neglect after a first, ischemic or haemorrhagic, right-hemispheric stroke (aged between 27 and 82, mean = 60.54, *SD* = 13.58; 20 women; mean years of education = 12.05, *SD* = 3.19) were included in the study after giving written, informed consent. Fig. 1 shows an overlap map of the lesions of all patients included in the study. Diagnosis of neglect was based on performance in the following tasks (all printed on A3 sheets of paper, in landscape orientation): (1) The Line Bisection Task (Wilson et al., 1987). A mean relative rightward deviation equal to or greater than 11% from the actual midline was considered as clinically relevant (Wilson et al., 1987); (2) A cancellation task, i.e., The Bells test (Gauthier et al., 1989), the Star Cancellation test (Wilson et al., 1987), or the Random Shape Cancellation test (Weintraub and Mesulam, 1988). The Centre of Cancellation (CoC), i.e., the centre of mass of the spatial distribution of detected items, was used to assess neglect (Rorden and Karnath, 2010). The CoC allows quantifying neglect severity taking into account both the number of omissions and the spatial distribution of these omissions (Rorden and Karnath, 2010). Furthermore, calculating the CoC also allows comparing the same indicator across the different cancellation tasks. A CoC value of 0 indicates an unbiased spatial distribution; positive CoC values indicate a shift towards the right side of space, while negative CoC values indicate a shift towards the left side of space. CoC values larger than 0.08 were considered as clinically relevant (Rorden and Karnath, 2010). Patients who fulfilled the criterion for clinical significance in at least one of the tests were considered as presenting with visual neglect, and were thus included in the study.

Twenty healthy controls were matched to the patient group with respect to age, sex, and years of education (aged between 51 and 82, *M* = 65.75, *SD* = 9.05; 11 women; mean years of education = 12.55,