CORTEX XXX (2017) 1–10

Available online at www.sciencedirect.com

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Journal homepage: www.elsevier.com/locate/cortex

Special issue: Research report

The role of left insula in executive set-switching: Lesion evidence from an acute stroke cohort

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ARTICLE INFO

Article history:
Received 30 March 2017
Reviewed 19 May 2017
Revised 18 July 2017
Accepted 13 November 2017
Published online xxx

Keywords:
Executive functions
Trail Making Test
Stroke
Set-switching
Lesion-symptom mapping

ABSTRACT

Impairments in executive functions are common in stroke survivors, both in the acute and in the chronic phase. However, little is known about the underlying lesion neuroanatomy of these deficits. This study aimed to elucidate the pattern of brain damage underlying executive dysfunction in a large and acute stroke cohort. Executive set-switching deficits were evaluated by a shape-based analogue of the Trail Making Test (from the Oxford Cognitive Screen) in a consecutive sample of 144 stroke patients (age: 70 ± 15 years, examination: 5 ± 4 days post-stroke; brain imaging: 1.7 ± 2.9 days post-stroke). A voxelwise lesion-symptom mapping analysis was performed by combining executive set-switching accuracy scores with manually delineated lesions on computerized tomography or magnetic resonance imaging scans. The analysis showed that lesions within the left insular cortex and adjacent white matter predicted poorer executive set-switching. Further analyses confirmed that the lesion effect in the left insula survived correction for the low-level visuospatial and motor component processes of executive set-switching. In conclusion, the study provides lesion-based evidence for the role of the left insular cortex in flexible switching of attention. The findings are consistent with emergent models of insular function postulating the role of this region in regulatory aspects of goal-directed behaviour.

1. Introduction

Flexible switching of attention between tasks, operations and stimulus sets reflects a core aspect of executive control (Miyake et al., 2000). Deficits in executive set-switching have been documented in both acute (Tamez et al., 2011) and chronic stroke cohorts (Chan et al., 2015; Yochim, Baldo, Nelson, & Delis, 2007). Mounting evidence highlights the importance of studying executive deficits that accompany stroke. For instance, a modulatory relationship between domain-general executive control mechanisms and domain-

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https://doi.org/10.1016/j.cortex.2017.11.009

specific cognitive tasks has been observed within language (Brownsett et al., 2014) and visuo-spatial attention domains (e.g., Robertson et al., 1997; Singh-Curry & Husain, 2009). Further, the presence of an early executive impairment may predispose stroke survivors for experiencing reduced quality of life in the chronic phase (Nys et al., 2006).

A commonly used instrument for mapping executive deficits in neurological populations is the Trail Making Test (TMT), a visuo-motor search task that induces switching between competing stimulus sets (e.g., Sánchez-Cubillo et al., 2009). Due to its purported executive demands (e.g., Arbuthnott & Frank, 2000; Kortte, Horner, & Windham, 2002), early lesion research speculated that the TMT may be used as a tool for detecting executive impairment stemming from frontal lesions (Stuss et al., 2001). However, several recent studies did not support the specific role of the frontal areas in mediating set-switching in the TMT, both in (sub)acute (<3 months; Tamez et al., 2011; Muir et al, 2015) and chronic phases post-stroke (>3 months, Chan et al., 2015; Muir et al., 2015). Specifically, these studies failed to demonstrate that patient categorisation, either into frontal versus non-frontal groups (Chan et al., 2015; Tamez et al., 2011), or based on the stroke involvement with the nodes of a predefined "executive network" (Muir et al., 2015), discriminated between the TMT-derived indices of set-switching.

By contrast, studies utilising a more sensitive approach of categorising patients based on the presence of a lesion in a voxel-wise fashion (see Bates et al., 2003; Rorden, Karnath, & Bonilha, 2007), suggest the involvement of diverse frontal regions in TMT performance. For instance, a large sample study of chronic brain-injured patients (N = 236) found that lesions within the rostral anterior cingulate cortex predicted less efficient set-switching performance (Gläscher et al., 2012). Another large-sample study of individuals with penetrating head injuries (N = 182) reported an association between regionally non-specific lesions within the left prefrontal cortex, anterior cingulate, insula, parietal and temporal areas and lower executive functioning, as evaluated by the Delis-Kaplan Executive Function System (D-KEFS) tests that included the TMT (Barbey et al., 2012). Furthermore, damage to the left dorsomedial prefrontal cortex was associated with slower set-switching in a study of 27 frontal chronic brain-injured patients with heterogeneous aetiologies (Miskin et al., 2016). Finally, lesions within the right dorsolateral prefrontal cortex predicted higher incidence of set-switching errors in a sample of 30 acute, right-hemispheric and predominantly frontal stroke patients (Kopp et al., 2015). Although these voxel-lesion-symptom mapping (VLSM) studies collectively suggest that frontal areas are important for executive set-switching, the regionally specific frontal contributions remain inconclusive. In addition, the use of chronic brain-injured samples or small sample sizes in these studies makes it difficult to tease apart the contributions of localised brain damage from the long-term spontaneous plasticity effects (see Gillebert & Mantini, 2013; Guerra-Carrillo, Mackey, & Bunge, 2014; Pascual-Leone, Amedi, Fregni, & Merabet, 2005).

Neuroimaging studies of the TMT performed in healthy volunteers suggest that both frontal and non-frontal areas are important for executive set-switching. Specifically, functional magnetic resonance imaging (fMRI) adaptations of the TMT contrasted the set-switching to a control condition and revealed brain activations in the prefrontal cortex, including the left lateral prefrontal cortex (Moll, de Oliveira-Souza, Moll, Bramati, & Andreiuolo, 2002), left superior frontal gyri (Zakzanis, Mraz, & Graham, 2005) and right-lateralised ventrolateral prefrontal cortex (Jacobson, Blanchard, Connolly, Cannon, & Garavan, 2011). Further, less consistent non-frontal contributions to the set-switching component of the TMT were also observed across these studies, including insular, parietal and temporal activations. In line with this, fMRI studies that utilised established switching paradigms, including task-switching (Dreher, Koechlin, Ali, & Grafman, 2002), stimulus-response reversal (Dove, Pollmann, Schubert, Wiggins, & von Cramon, 2000), and the Wisconsin Card Sorting Task (Monchi, Petrides, Petre, Worsley & Dagher, 2004), implicated a widely distributed circuitry of both frontal and non-frontal regions in executive set-switching. Indeed, two meta-analyses of set-switching reported converging evidence that in healthy individuals, set-switching operations engage a widespread neural circuitry comprising superior parietal, premotor and anterior insular regions in addition to consistently reported prefrontal activation effects (Derrfuss, Brass, Neumann, & Cramon, 2005; Wager, Jonides, & Reading, 2004).

Overall, although neuroimaging findings suggest that executive set-switching performance is mediated by a circuitry that extends beyond prefrontal cortex, a high regional variability of the reported effects makes it difficult to synthesise the findings across the studies. In addition, while VLSM studies highlight the involvement of the prefrontal cortex in executive set-switching in chronic brain-injured cohorts (Barbey et al., 2012; Gläscher et al., 2012; Miskin et al., 2016), lesion-mapping studies of executive deficits in acute stroke patients are lacking. The only identified VLSM study of executive set-switching in an acute stroke cohort used a restrictive sampling criteria based on the anatomical lesion location and included 30 patients (Kopp et al., 2015).

The current study aimed to elucidate the neuroanatomical underpinnings of executive set-switching deficits in a large (N = 144), consecutive, and acute stroke sample. Executive set-switching performance was quantified by a shape-based TMT analogue included in the Oxford Cognitive Screen (OCS) (Demeyere, Riddoch, Slavkova, Bickerton, & Humphreys, 2015), a stroke-specific screening tool covering the domains of attention and executive function, language, memory, praxis and number processing. In contrast to the standard TMT, which requires number-letter switching, the shape-based TMT analogue requires alternation between task-relevant shapes in order of size. The shape-based TMT analogue is intended to provide a more sensitive screen of executive deficits in stroke, as it permits assessing patients who are impaired in language and/or numerical sequencing (Demeyere et al., 2015). We used a voxel-wise approach (Bates et al., 2003) to map acute lesion data (mean stroke to scan interval = 2 days) onto acutely evaluated executive set-switching deficits (mean stroke to test interval = 5 days). The use of an acute stroke sample allowed the interrogation of lesion-deficit coupling in the absence of confounding long-

Please cite this article in press as: Varjačić, A., et al., The role of left insula in executive set-switching: Lesion evidence from an acute stroke cohort, Cortex (2017), https://doi.org/10.1016/j.cortex.2017.11.009