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Cognitive reserve and cognitive performance of patients with focal frontal lesions

Sarah E. MacPherson[a,b], Colm Healy[c], Michael Allerhand[a,b], Barbara Spanò[d], Carina Tudor-Sfetea[c], Mark White[e], Daniela Smirni[f], Tim Shallice[g,h], Edgar Chan[c], Marco Bozzali[d], Lisa Cipolotti[c,f,*]

[a] Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK
[b] Department of Psychology, University of Edinburgh, Edinburgh, UK
[c] Department of Neuropsychology, National Hospital for Neurology and Neurosurgery, London, UK
[d] Neuroimaging Laboratory, Santa Lucia Foundation, Rome, Italy
[e] Department of Neuroradiology, National Hospital for Neurology and Neurosurgery, London, UK
[f] Dipartimento di Scienze Psicologiche, Pedagogiche e della Formazione, Università degli Studi di Palermo, Palermo, Italy
[g] Institute of Cognitive Neuroscience, University College London, UK
[h] International School for Advanced Studies (SISSA-ISAS), Trieste, Italy

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ABSTRACT

The Cognitive reserve (CR) hypothesis was put forward to account for the variability in cognitive performance of patients with similar degrees of brain pathology. Compensatory neural activity within the frontal lobes has often been associated with CR. For the first time we investigated the independent effects of two CR proxies, education and NART IQ, on measures of executive function, fluid intelligence, speed of information processing, verbal short term memory (vSTM), naming, and perception in a sample of 86 patients with focal, unilateral frontal lesions and 142 healthy controls. We fitted multiple linear regression models for each of the cognitive measures and found that only NART IQ predicted executive and naming performance. Neither education nor NART IQ predicted performance on fluid intelligence, processing speed, vSTM or perceptual abilities. Education and NART IQ did not modify the effect of lesion severity on cognitive impairment. We also found that age significantly predicted performance on executive tests and the majority of our other cognitive measures, except vSTM and GNT. Age was the only predictor for fluid intelligence. This latter finding suggests that age plays a role in executive performance over and above the contribution of CR proxies in patients with focal frontal lesions. Overall, our results suggest that the CR proxies do not appear to modify the relationship between cognitive impairment and frontal lesions.

1. Introduction

It is well known that the cognitive response to brain damage caused by stroke, tumour, trauma, dementia and/or age-related changes can vary across individuals to a considerable degree (e.g., Stern, 2009; Lindenberger et al., 2013). The Cognitive Reserve (CR) hypothesis was put forward to account for some of the reported variability in cognitive performance and suggests that the effects of age-related changes or brain damage can be mitigated by the premorbid efficiency, capacity and flexibility of cognitive processing (e.g., Stern, 2002; Jones et al., 2011; Barulli and Stern, 2013; Levi et al., 2013). It has also been proposed that the effectiveness of cognitive processing can be shaped by life experiences (Stern, 2012). Several proxies have been used to estimate CR. These are thought to 'protect' against the impact of brain damage and include: education, socio-economic status, occupational achievement and engagement in cognitively and socially stimulating activities (Suchy et al., 2011; Levi et al., 2013; Liu et al., 2013; Okonkwo et al., 2014; for a review see Arenaza-Urquijo et al., 2015).

The most commonly used proxy of CR is education (e.g., Bennett et al., 2003; Farfel et al., 2013; Sumowski et al., 2013). Education encompasses the accumulated knowledge and skills gained through formal schooling. It is easy to quantify and has been shown to be a good predictor of healthier lifestyle and economic prosperity (e.g., Mirowsky and Ross, 2005). In patients with similar levels of pathology, high education has been associated with less cognitive impairment than in patients with low education (e.g., Bennett et al., 2003; Ngandu et al.,

* Corresponding author at: Department of Neuropsychology, National Hospital for Neurology and Neurosurgery, Queen Square, London WC1N 3BG, UK.
E-mail address: l.cipolotti@ucl.ac.uk (L. Cipolotti).

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2007; Roe et al., 2007). Another proxy of CR is literacy attainment, often assessed using the National Adult Reading Test (NART; Nelson and Willison, 1991) or other single word reading tests, as they are assumed to reflect premorbid intelligence (Wiens et al., 1993). Higher NART IQ has been associated with greater CR capacity (Tucker and Stern, 2011; Stern, 2012).

The concept of CR has been investigated primarily in neurodegenerative disorders, traumatic brain injury and healthy aging. Several studies have reported that individuals with similar brain pathology demonstrate differences in their cognitive impairment, depending on whether they have higher or lower levels of education and/or NART IQ (e.g., Grafman et al., 1986; Bennett et al., 2003; Stern, 2006; Singh-Manoux et al., 2011; Serra et al., 2014; Bozzali et al., 2015). For example, low education increases the risk of dementia whilst high education and NART IQ protects against dementia, particularly the onset of Alzheimer's disease (AD, Schmand et al., 1997; Meng and D'Arcy, 2012; Lo, and Jagust, 2013; see for a review Xu et al., 2015). High education has been shown to attenuate the decline in attention, speed and memory performance in patients with multiple sclerosis (Sumowski et al., 2014). Raymont et al. (2008) reported that higher pre-morbid intelligence, assessed using the armed forces qualification test, was the strongest deterrent against cognitive decline in patients with penetrating head injury.

However, few studies have investigated the effects of CR on cognitive performance in aetiologies such as stroke (for a review see Nunnari et al., 2014) or brain tumour where the lesions are focal compared to the diffuse lesions associated with slow progressive diseases such as Alzheimer's disease. In stroke, it has been reported that education protects against global cognitive decline (e.g., Sachdev et al., 2004; Elkins et al., 2006; Zieren et al., 2013) or severity of aphasia (González-Fernández et al., 2011). In brain tumour, although data have not been reported to suggest that education can attenuate cognitive impairment, age and tumour location (frontal) have been shown to predict cognitive outcome on speed, executive and working memory tasks (Kaleita et al., 2004).

Relatively little is known about whether CR may differentially affect performance on different cognitive measures. There is some preliminary evidence suggesting that certain cognitive abilities may be more susceptible than others to the mitigating effects of CR. *High education* has been associated with better performance in stroke patients on tests of language, perception and memory, but not executive functioning, once white matter integrity had been taken into account (Ojala-Oksala et al., 2012). Higher rates of decline in AD patients with *lower education* have been reported on memory and executive tasks but not abstract reasoning, visual-spatial skills or language (Scarmeas et al., 2006).

Importantly, the relationship between CR and different cognitive measures may also be dependent on the proxy used to estimate CR. In a large cohort study including healthy older adults and patients with possible dementia, Jefferson et al. (2011) found that education was primarily related to performance on global cognition, episodic and semantic memory, and perception. In contrast, NART IQ was found most strongly associated with working memory but also global cognition and episodic memory. Siedlecki et al. (2009) found no significant correlation between education and NART IQ in healthy controls and suggested that these two proxies may account for different elements of the variance in cognitive performance. Using path analysis on data from the MRC National Survey of Health and Development cohort, Richards and Sacker (2003) demonstrated three independent paths from childhood cognition, and educational and occupational attainment to CR using the NART as an index. Furthermore, when examining the relationships between brain volume and CR proxies in healthy adults over a two-year period, Persson et al. (2016) reported that larger baseline brain volumes predict greater increases in fluid intelligence. In contrast, no relationships between literacy attainment and brain volumes were found. Researchers have argued that more than one CR proxy measure should be considered, as CR is the result of a combination of life experiences and activities (e.g., Stern, 2009; Tucker and Stern, 2011). One CR proxy is unlikely to provide an absolute measure of CR. A recent meta-analysis examining the influence of education, occupational attainment, and involvement in cognitively stimulating activities (e.g., crosswords, playing bridge) in healthy individuals demonstrated that while different CR proxies are associated with one another, they also offer a unique contribution to CR (Opdebeeck et al., 2016).

The effects of CR may also be dependent on the specific brain regions that are damaged. For example, Robertson (2014) suggested that the structural and functional integrity of the lateral surface of the right prefrontal cortex and/or the right inferior parietal cortex may play a crucial role in CR. Higher levels of CR have also been associated with the concept of scaffolding, a lifelong process that involves the use and development of complementary, alternative neural circuits to achieve a particular cognitive goal (Alexander et al., 1997; Perneczky et al., 2006). The concept of scaffolding has been developed in the theoretical context of the Scaffolding Theory of Aging and Cognition (STAC) suggesting that, in healthy aging and in pathological brain damage, scaffolding can compensate for cognitive decline (Reuter-Lorenz and Park, 2014). Importantly, Park and Reuter-Lorenz (2009) proposed that scaffolding processes largely reside in the prefrontal cortex. Thus, damage to the prefrontal cortex may have a detrimental effect on the compensation provided by CR.

Surprisingly, the studies conducted so far have not investigated whether there are specific brain areas critical for CR. The non-specific nature of brain-related changes in neurodegenerative diseases, traumatic brain injury and healthy aging limits our ability to draw conclusions as to which specific brain areas may contribute to CR. Examination of patients with more focal brain lesions, such as those resulting from stroke and tumour, may overcome such limitations. However, the stroke and tumour studies conducted so far have included patients with lesions not restricted to specific cortical areas. Thus, the high degree of variability in the patients' cognitive performance inevitably reduces one's ability to draw conclusions regarding the interaction between CR and brain lesion.

To our knowledge, our study is the first to investigate the independent effects of education and NART IQ on measures of executive function, fluid intelligence, speed of information processing, verbal short term memory (vSTM), naming and perception in a large sample of patients with focal, unilateral frontal lesions. Our study also investigated for the first time whether CR might safeguard against focal neuropathology and moderate cognitive impairment across these various cognitive measures.

2. Material and methods

2.1. Participants

Data from 164 patients who had attended the Neuropsychology Department of the National Hospital for Neurology and Neurosurgery, Queen Square, London, were retrospectively screened for study eligibility. All patients had a unilateral lesion confined to the frontal region resulting from stroke or brain tumour. All tumour patients had undergone lesion resection prior to neuropsychological assessment. Our exclusion criteria were: i) age at the time of cognitive testing ≥80 years due to the availability of age-matched healthy control data and standardised age norms; ii) current or previous psychiatric disorders; iii) previous neurological disorders including strokes or tumours; iv) presence of metastatic tumours; v) previous chemotherapy; vi) gross visual (i.e., cortical blindness), perceptual (i.e., neglect; agnosia), motor (i.e., hemiplegia) or language (i.e., dysphasia) impairment; vii) previous head trauma; viii) history of alcohol or drug abuse; ix) no MRI or CT scan results available; x) no or limited neuropsychological data available; xi) a score < 5th percentile on a test of general intelligence