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The effect of age on cognitive performance of frontal patients

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ABSTRACT

Age is known to affect prefrontal brain structure and executive functioning in healthy older adults, patients with neurodegenerative conditions and TBI. Yet, no studies appear to have systematically investigated the effect of age on cognitive performance in patients with focal lesions. We investigated the effect of age on the cognitive performance of a large sample of tumour and stroke patients with focal unilateral, frontal ($n=68$), or non-frontal lesions ($n=45$) and healthy controls ($n=52$). We retrospectively reviewed their cross sectional cognitive and imaging data. In our frontal patients, age significantly predicted the magnitude of their impairment on two executive tests (Raven's Advanced Progressive Matrices, RAPM and the Stroop test) but not on nominal (Graded Naming Test, GNT) or perceptual (Incomplete Letters) task. In our non-frontal patients, age did not predict the magnitude of their impairment on the RAPM and GNT. Furthermore, the exacerbated executive impairment observed in our frontal patients manifested itself from middle age. We found that only age consistently predicted the exacerbated executive impairment. Lesions to specific frontal areas, or an increase in global brain atrophy or white matter abnormalities were not associated with this impairment. Our results are in line with the notion that the frontal cortex plays a critical role in aging to counteract cognitive and neuronal decline. We suggest that the combined effect of aging and frontal lesions impairs the frontal cortical systems by causing its computational power to fall below the threshold needed to complete executive tasks successfully.

1. Introduction

It is well-recognised that healthy aging is associated with a decline in cognitive processes. Research has shown that self-initiated frontal 'executive' processes appear to be the most affected (Craik, 1986) with the greatest anatomical changes found in the prefrontal cortex (PFC) compared with other cortical regions (e.g., O'Sullivan et al., 2001; MacPherson et al., 2002; West et al., 2002). Specifically, healthy older individuals have reduced cortical volume, increased white matter abnormalities (WMA) and functional over- or under-activation have all been documented in the PFC compared with young individuals (e.g., Cabeza, 2002; Raz et al., 2005; Sullivan and Pfefferbaum, 2006; Fjell et al., 2009; Head et al., 2009). These structural abnormalities are correlated with poorer executive performance (e.g., Nagahama et al., 1997; Gunning-Dixon and Raz, 2003; Van Petten et al., 2004; Raz et al., 2007; Cardenas et al., 2011). For example, increased WMA and smaller anterior cingulate cortex volume are associated with poorer performance on the Stroop test and fluid intelligence tasks (e.g., Raz et al., 2007; Elderkin-Thompson et al., 2008, but see Salthouse (2011)).

Abbreviations: PFC, prefrontal cortex; WMA, white matter abnormalities; TBI, traumatic brain injury; IQ, Intelligence Quotient; CVA, cerebrovascular accident; HC, healthy controls; NART, National Adult Reading Test; RAPM, Raven's Advanced Progressive Matrices; GNT, Graded Naming Test; IL, Incomplete Letters and; CWMA, Composite White Matter Abnormalities

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Similarly, pathological aging research, involving individuals such as those with dementia or other neurological conditions, has shown a decline in executive performance together with structural and functional changes in the PFC (e.g., Pachana et al., 1996; Matsuo et al., 2008; Debette and Markus, 2010; for a review see Cabeza and Dennis (2013)). This decline is thought to reflect 'accelerated normal aging', a process resembling normal aging but occurring earlier and faster, as a result of brain pathology (Buckner, 2004). Accelerated cognitive aging has also been documented following traumatic brain injury (TBI; e.g., Corkin et al., 1989). For example, older Vietnam veterans with penetrating head injury lesions involving the frontal lobes (although not exclusively) showed a greater decline in IQ than younger veterans (Raymont et al., 2008). Moreover, the effect of aging on TBI patients' appears to specifically affect executive (Stroop test) performance but not verbal memory performance (Klein et al., 1996).

However, the non-specific nature of brain-related changes in neurodegenerative diseases and TBI limits our ability to draw firm conclusions that age moderates lesion-related impairment in executive functions. Examination of patients with more focalised frontal and non-frontal lesions such as those resulting from stroke and tumour would overcome such limitations. A meta-analysis has hinted that age disproportionately affects performance on executive tasks in patients with frontal lesions (Alvarez and Emory, 2006). However, this review included patients with less focal lesions due to TBI, epilepsy, gunshot wounds and encephalitis, and a surprisingly small number of stroke ($n=14$) and tumour patients ($n=1$).

Older stroke and tumour patients have consistently been associated with higher mortality rates, poorer functional outcomes and general cognitive decline (e.g., Appelros et al., 2003; Nakayama et al., 1994; Patel et al., 2002; Yoshii et al., 2008). In stroke age has been associated with greater executive impairment (e.g., Pohjasvaara et al., 2002; Oksala et al., 2009) together with WM abnormalities and/or cortical atrophy (e.g., Jokinen et al., 2005; Kooistra et al., 2014). In brain tumour, middle-aged (36–59 years) and older (60+ years) patients performed more poorly than younger patients (<35) on a test of 'executive' function and information processing (Trail Making B; Kaleita et al., 2004; however, see Chan et al. (2014)). However, given the absence of a healthy control sample, it remains unclear whether the executive impairments in stroke and tumour reflect typical age-related decline or an exacerbated executive impairment. Furthermore, in these studies, the lesions in the stroke and tumour patients were 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 age, brain lesion and executive functioning.

To the best of our knowledge, no previous study has systematically examined the effects of age on cognitive performance in patients with focal lesion. The aim of our study was to investigate the effect of age on 'executive', nominal and perceptual tasks in a large sample of patients with focal, unilateral, frontal or non-frontal lesions and healthy controls. Structural data included the classification of frontal lesions in 4 major anatomical areas, measures of global brain atrophy and WM abnormalities.

2. Methods

2.1. Participants

Data from 122 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 or non-frontal brain regions resulting from a cerebrovascular accident (CVA; stroke) or a brain tumour. All tumour patients had undergone tumour resection prior to neuropsychological assessment. Our exclusion criteria were as follows: i) age at the time of cognitive testing >80 years due to the availability of age matched healthy control data and standardised age norms for patients up to 80 years, ii) current or previous psychiatric disorders, iii) previous neurological disorders including CVAs 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 neuropsychological data available, and xi) a score below the 5th percentile on a test of general intelligence (WAIS-III, Wechsler, 1997; WAIS-R, Wechsler, 1981; or Raven's Matrices, Raven, 1976). Non-native English speakers were only included in the study if they obtained a score at or above the 25th%ile on the National Adult Reading Test (NART, Nelson, 1982). This was to ensure that their English abilities were sufficient to cope with task demands.

Application of these exclusion criteria resulted in data from nine patients being removed ($n=1$ history of psychiatric disorder; $n=3$ history of neurological disorder; $n=1$ previous chemotherapy; $n=1$ hemiplegia; $n=1$ expressive dysphasia). Data from 68 frontal patients (38 males and 30 females) and 45 non-frontal patients (24 males and 21 females) were included in the study. The aetiologies of the frontal lesions were as follows: stroke (CVA, $n=17$); high-grade tumours ($n=15$); low-grade tumours ($n=14$); and meningioma ($n=22$). Thirty seven frontal patients had left hemisphere lesions and 31 had right hemisphere lesions. The mean time between damage and assessment for the frontal patients was 16.41 months (standard deviation (SD)=33.80 months). Five frontal patients had reported hemiparesis and 3 frontal patients had hemianopia. Other clinical and cognitive aspects of the frontal patients have been previously reported (MacPherson et al., 2010; Robinson et al., 2012, 2015; Murphy et al., 2013). Importantly for the current study, we have previously documented no significant differences in the performance of CVA, high- or low-grade tumour, or meningioma on the Raven's Advanced Progressive Matrices, Stroop Colour-Word and Graded Naming Tests. This suggests that the grouping together of frontal patients with different aetiologies is methodologically justifiable (Cipolotti et al., 2015).

The aetiologies of the non-frontal patients were as follows: stroke (CVA, $n=13$); high-grade tumours ($n=10$); low-grade tumours ($n=10$); and meningioma ($n=12$). Twenty-two non-frontal patients had left hemisphere lesions and 23 had right hemisphere lesions. The mean time between damage and assessment for the non-frontal patients was 17.40 months (SD=38.46 months). Three non-frontal patients had reported hemiparesis and 6 non-frontal patients had hemianopia.

Data from 52 healthy controls (HC) who did not significantly differ from the frontal and non-frontal patients in terms of age, gender, NART IQ and years of education were also reviewed (see Section 2.4.1). The study was approved by the National Hospital for Neurology and Neurosurgery and the Institute of Neurology joint Research Ethics Committee (UK).

2.2. Cognitive investigation

We retrospectively reviewed the cognitive performance of the patients and healthy controls on a single assessment comprising of well-known tests with published standardised normative data. For the frontal patients and healthy controls data was available on the following tests: National Adult Reading Test (NART; Nelson, 1982) used to estimate optimal pre-morbid functioning; the Raven's