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The impact of different aetiologies on the cognitive performance of frontal patients

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ABSTRACT

Neuropsychological group study methodology is considered one of the primary methods to further understanding of the organisation of frontal 'executive' functions. Typically, patients with frontal lesions caused by stroke or tumours have been grouped together to obtain sufficient power. However, it has been debated whether it is methodologically appropriate to group together patients with neurological lesions of different aetiologies. Despite this debate, very few studies have directly compared the performance of patients with different neurological aetiologies on neuropsychological measures. The few that did included patients with both anterior and posterior lesions.

We present the first comprehensive retrospective comparison of the impact of lesions of different aetiologies on neuropsychological performance in a large number of patients whose lesion solely affects the frontal cortex. We investigated patients who had a cerebrovascular accident (CVA), high (HGT) or low grade (LGT) tumour, or meningioma, all at the post-operative stage. The same frontal 'executive' (Raven's Advanced Progressive Matrices, Stroop Colour-Word Test, Letter Fluency-S; Trail Making Test Part B) and nominal (Graded Naming Test) tasks were compared. Patients' performance was compared across aetiologies controlling for age and NART IQ scores. Assessments of focal frontal lesion location, lesion volume, global brain atrophy and non-specific white matter (WM) changes were undertaken and compared across the four aetiology.

We found no significant difference in performance between the four aetiology subgroups on the 'frontal' executive and nominal tasks. However, we found strong effects of premorbid IQ on all cognitive tasks and robust effects of age only on the frontal tasks. We also compared specific aetiology subgroups directly, as previously reported in the literature. Overall we found no significant differences in the performance of CVA and tumour patients, or LGT and HGT patients or LGT, HGT and meningioma's on our four frontal tests. No difference was found with respect to the location of frontal lesions, lesion volume, global brain atrophy and non-specific WM changes between the subgroups.

Our results suggest that the grouping of frontal patients caused by different aetiologies is a pragmatic, justified methodological approach that can help to further understanding of the organisation of frontal executive functions.

1. Introduction

Neuropsychological group study methodology is considered one of the primary methods to further understanding of the neuroanatomical architecture underlying cognitive functions. However, to obtain sufficient power with this methodology it is necessary to recruit rather large numbers of neurological patients. If too few patients are used, the results are inevitably inconclusive. Thus, to investigate neuro-cognitive architectures, patients with different aetiologies such as vascular (CVA) or tumour (different types of brain tumours) are often combined. A typical example of this approach is given by research investigating the organisation of frontal 'executive' functions. Different aspects of executive

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functioning have been explored in influential studies grouping patients with frontal lesions caused by stroke or tumours. Thus, Stuss et al. (2003) investigated a measure of executive control combining patients with CVA ($n=19$) and patients with either tumour or lobectomy ($n=12$). Roca et al. (2010) investigated fluid intelligence and executive functions in a group which combined 11 CVA and 31 tumour patients. Robinson et al. (2012) investigated verbal generation in a group combining 15 CVA and 52 tumour patients.

However, it is well known that stroke and tumours affect brain structures in several different ways. For example, CVAs such as ischaemic stroke causes cell death within the affected area. In contrast, neural activity can persist in areas infiltrated by low grade tumours (e.g. Krainik et al., 2003). The onset of a CVA is defined by an acute event; the rate of brain tumour growth can vary dramatically by grading (see, e.g. Jääskeläinen et al., 1985; Kleihues et al., 2007, p. 36). Physical changes in brain structures resulting from different grades of brain tumour are not equivalent. For example, low grade tumours and meningioma's are likely to compress adjacent brain structures (Perry et al., 2007). In contrast, high grade tumours such as glioblastomas are likely to invade cortical or subcortical structures (Kleihues et al., 2007). These fundamental differences raise the possibility that CVA, high grade tumours, low grade tumours and meningioma's may recruit mechanisms of neural plasticity in different ways leading to different functional outcomes.

In the literature it has been debated if, for the purpose of neuropsychological investigation, the grouping together of patients with different neurological aetiologies is methodologically appropriate (e.g. Duffau, 2011: Clinical Neuroanatomy, discussion forum, Cortex). For example, Anderson et al. (1990) argued that as far as stroke and tumour patients are concerned "…the two patient types should be treated separately for the purpose of neuropsychological research". Karnath and Steinbach (2011) focused on tumour patients (unilateral gliomas or meningiomas) and argued that neuropsychological investigation should not "…use patients with tumours to identify the 'critical lesion sites' related to a certain disorder, in particular if the more general aim is to determine the neural representation of this function in the human brain…" (p. 1005). In contrast, Shallice et al. (2010) reported that patients with different aetiologies give rise to the same localisation of a critical function (for example see Brambati et al. (2006) and Campanella et al. (2010), naming of non-living objects).

Despite this debate, very few studies have directly compared the performance of patients with different neurological aetiologies on neuropsychological measures. Only Anderson et al. (1990) have compared stroke and tumour patients and attempted to control for lesion location. The authors investigated the neuropsychological performance of a relatively small sample of stroke ($n=19$; 10 left, 9 right) and tumour (8 left, 9 right; glioma, grade unknown $n=15$; meningioma $n=2$) patients. Using mainly CT scans, the investigators attempted to match anatomically the patients for lesion size and location on a case-by-case basis. The authors reported that the left stroke patients performed significantly worse than the left tumour patients on 4/6 subtests from the Multilingual Aphasia Examination battery. For right hemisphere patients, differences were less clear cut (see Shallice et al. (2010) for discussion).

Other studies have investigated whether patients with high and low grade tumours differ in terms of neuropsychological test performance (Hom and Reitan, 1984; Hahn et al., 2003). Unfortunately, the effect of lesion location at a finer level than the hemisphere has generally not been reported. In an older study, Hom and Reitan (1984) compared patients with high grade tumours (grade ≥ 3, $n=46$) and with low-grade tumours (grade ≤ 2, $n=46$) on the WAIS-III and Halstead–Reitan battery. High grade performed worse than low grade tumour patients on the WAIS-III and almost all the subtests of the Halstead–Reitan battery. Similarly, Hahn et al. (2003) reported that high grade ($n=31$) performed significantly poorer than low grade tumour patients ($n=37$) on two out of ten neuropsychological measures (Trail-Making Test Part A, COWAT FAS). Shallice et al. (2010) studied the effect of type of tumour on four different 'right parietal' tests. They investigated high grade tumour patients ($n=25$), low grade tumour patients ($n=28$) and meningioma patients ($n=15$). The authors reported that in two of the four tests, high grade tumour patients performed significantly worse than low grade tumour patients post-operatively. However, there was a significant post-operative decline in three tests in the low grade tumour group.

In contrast, other studies have reported no significant differences between high and low grade tumour patients on extensive batteries of tests. Scheibel et al. (1996) contrasted patients with highly malignant glioblastomas (grade 4, $n=106$) and less malignant gliomas (grade ≤ 3, $n=139$), with all patients at the post-operative stage. No effect of tumour malignancy was found, although significant effects for tumour lateralisation and type of therapy (radiotherapy, resection or both) were reported. Talacchi et al. (2011) also documented no significant difference in performance in a small number of high and low grade post-operative tumour patients ($N=17$ and $N=12$, respectively).

It should be noted that none of the studies reviewed above attempted a comprehensive comparison between aetiologies, such as vascular and different type and grades of tumours. It is often unclear whether studies reporting on tumour patients were tested at the pre-operative or post-operative stage. All previous studies have included patients with both anterior and posterior lesions. Moreover, most did not characterize lesion location at a finer level than the damaged hemisphere, the only exception being the study by Shallice et al. (2010). Lesion size comparisons have only been documented by the Anderson et al. (1990) study using mainly CT scans. Interestingly, only some of the studies have analysed and corrected for the effect of age (Hahn et al., 2003; Scheibel et al., 1996). Others have not and yet reported difference between the age of the aetiology groups (e.g. CVA patients older than tumour patients, Anderson et al., 1990; high grade glioma patients older than low grade glioma patients, Hom and Reitan, 1984).

The aim of our retrospective study was to carry out the first comprehensive comparison of the impact of different aetiologies on neuropsychological performance. We reviewed a large number of patients with CVA; high and low grade tumours as well as meningiomas, all at the post-operative stage. The lesions of all patients were unilateral and confined to the frontal lobes. We determined the location of the frontal lesions and for a subsample of patients the total lesion volume. Measures of global atrophy and white matter (WM) changes were also undertaken. We compared the performance of the frontal patients on the same frontal 'executive' and nominal tasks across the aetiologies whilst taking into account differences in age and premorbid levels of functioning. Apriori comparisons of specific aetiologies groups were also conducted. Using these we sought to investigate further the findings of previous studies (Anderson et al., 1990; Hom and Reitan, 1984).

2. Materials and methods

2.1. Participants

One hundred and sixty four patients with a unilateral lesion confined to the frontal lobes resulting from a cerebrovascular accident (CVA) or a brain tumour, attending the Neuropsychology Department at the National Hospital for Neurology and Neurosurgery, Queen Square, London, were retrospectively screened for