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Cognitive reserve proxies do not differentially account for cognitive performance in patients with focal frontal and non-frontal lesions

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ABSTRACT

Objective: Cognitive reserve (CR) suggests that premorbid efficacy, aptitude and flexibility of cognitive processing can aid the brain's ability to cope with change or damage. Our previous work has shown that age and literacy attainment predict the cognitive performance of frontal patients on frontal-executive tests. However, it remains unknown whether CR also predicts the cognitive performance of non-frontal patients. **Method:** We investigated the independent effect of a CR proxy, NART IQ, as well as age and lesion group (frontal versus non-frontal) on measures of executive function, intelligence, processing speed and naming in 166 patients with focal, unilateral frontal lesions, 91 patients with focal, unilateral non-frontal lesions and 136 healthy controls. **Results:** Fitting multiple linear regression models for each cognitive measure revealed that NART IQ predicted executive, intelligence and naming performance. Age also significantly predicted performance on the executive and processing speed tests. Finally, belonging to the frontal group predicted executive and naming performance while membership of the non-frontal group predicted intelligence. **Conclusions:** These findings suggest that age, lesion group and literacy attainment play independent roles in predicting cognitive performance following stroke or brain tumour. However, the relationship between CR and focal brain damage does not differ in the context of frontal and non-frontal lesions.

Keywords: Cognitive reserve, Frontal lesion, Non-frontal lesion, Neuropsychological tests, Age, Aetiology

INTRODUCTION

Individuals who experience the same age-related changes or damage to the brain due to neurological conditions can vary greatly in their cognitive response (e.g., Stern, 2002, 2009; Lindenberger et al., 2013; Jokinen et al., 2016). The Cognitive Reserve (CR) hypothesis attempts to explain some of this variability. It suggests that premorbid efficacy, aptitude and flexibility of cognitive processing can aid the brain's ability to cope with change or damage (e.g., Stern, 2002; Jones et al., 2011; Barulli & Stern, 2013; Levi et al., 2013). Early environmental influences such as education and childhood socio-economic status (SES) have been found to be predictors of cognition in later life, suggesting those with higher education or SES might be less susceptible to cognitive decline because of their initially higher levels of cognition (Deary & Brett, 2015; Greenfield & Moorman, 2019). For example, education has been found to be related to overall cognition, episodic and semantic memory as well as perceptual abilities in older adults and adults with possible dementia (Jefferson et al., 2011). Further life experiences such as occupational achievement, literacy attainment and engagement in cognitively and socially stimulating activities are also known to play an important role in increasing the effectiveness of cognitive processing (Suchy et al., 2011; Stern, 2012; Levi et al., 2013; Liu et al., 2013; Okonkwo et al., 2014; for a review see Arenaza-Urquijo et al., 2015). Literacy attainment, a CR proxy often assessed using single word reading tasks such as the National Adult Reading Test (NART; Nelson & Willison, 1991), has been related to overall cognition, working memory and episodic memory (Siedlecki et al., 2009).

CR may explain some of the individual differences among the vulnerability to brain damage and may increase resistance to age- and disease-related brain changes (Jokinen et al., 2016). The heterogeneity of brain pathology presents a challenge for clinicians to be able to predict patients' cognitive outcomes, and following focal brain injury, better understanding of the mechanisms underlying recovery of cognitive function is important (Green et al., 2008).

CR continues to develop across the lifetime and so even late-stage interventions can potentially enhance CR to mitigate the effects of brain damage (Tucker & Stern, 2011). Research has shown that individuals with comparable levels of brain pathology demonstrate differences in their cognitive impairment, dependent on whether they have high or low educational attainment 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). Darby et al. (2017) found that higher years of education was related to performance on executive tasks in patients with mild cognitive impairment (MCI), but not Alzheimer's disease (AD), whereas higher years of education were associated with performance on semantic tasks in MCI and AD. Individuals with low levels of education are at a higher risk of dementia compared to individuals with higher levels of education, especially AD (Schmand et al., 1997; Meng & D'Arcy, 2012; Lo & Jagust, 2013; see for a review Xu et al., 2015).

Compared to diffuse lesions associated with degenerative conditions, few studies have examined the influence of CR on cognitive performance in neurological conditions that result in focal lesions such as stroke (see Nunnari et al., 2014) or brain tumour. CR may not have the same neuroprotective benefit in the context of focal brain damage due to brain tumour or stroke. In healthy and pathological aging, there may be more plasticity and functional reorganization due to their slow progressive nature (Morris, 2005; Ryan & Rossor, 2011). As stroke and tumour are associated with a more rapid disease process, they may have limited effects of CR proxies. Yet, in stroke, patients who received a higher number of years of formal education had less cognitive decline than stroke patients with fewer years of formal education (e.g., Sachdev et al., 2004; Elkins et al., 2006; Zieren et al., 2013; see Kessels et al., 2017 for a meta-analysis). Moreover, stroke patients with a higher number of years of formal education were found to have a lower risk of developing clinically diagnosed cognitive impairment (Kessels et al., 2017) and less severe aphasia (González-Fernández et al., 2011). Recently, Makin et al. (2018)

reported that NART IQ and years of education were better predictors of cognition post-stroke compared to vascular risk factors or stroke severity.

Yet, to our knowledge, CR studies have not examined whether particular brain areas are responsible for the ability to compensate for brain damage. CR has been associated with the scaffolding theory of aging and cognition (STAC; Park & Reuter-Lorenz, 2009). Scaffolding is a process that takes place throughout the lifespan and involves the formation and enhancement of existing and new neural connections to achieve specific cognitive goals (Alexander et al., 1997; Pernecky et al., 2006). In healthy aging and neurodegenerative diseases, higher levels of CR are thought to result in more effective scaffolding as compensation for cognitive decline (Reuter-Lorenz & Park, 2014). Research suggests that both CR and scaffolding are thought to rely on the integrity of the prefrontal cortex (Park & Reuter-Lorenz, 2009; Robertson, 2014; see Anthony & Lin, 2017 for a review of the neuroimaging literature). Therefore, the prefrontal cortex may be a potential brain area for sustaining the ability to protect or compensate for cognitive decline.

Neuroimaging studies have also provided evidence of potential neural substrates for CR, including the frontal lobes. For example, a review of PET studies by Morbelli and Nobili (2014) found that AD patients with high CR tend to show hypermetabolism in the dorsolateral prefrontal cortex but hypometabolism in the temporo-parietal cortex. Studies examining CR based on education have reported greater frontal lobe thickness associated with higher education (Vaqué-Alcázar et al., 2017); with greater loss in the left anterior cingulate cortex and left dorsomedial prefrontal cortex in individuals with exceptionally low years of education (Rzezak et al., 2015). However, other studies examining CR have shown higher occupation, socioeconomic status, and leisure activities are associated with less hippocampal atrophy (Staff et al., 2012; Suo et al., 2012). In large cohort studies, education but not occupation or leisure

activities significantly correlates with frontal and parieto-temporal regions (Foubert-Samier et al., 2012).

If the prefrontal cortex plays a role in CR, lesions in the prefrontal cortex should reduce the ability to compensate for brain damage. Therefore, patients with prefrontal lesions are less likely to demonstrate differences in their cognitive impairment depending on whether they have higher or lower levels of education and/or NART IQ. Yet, few studies have examined CR in patients with lesions restricted to specific cortical areas. While higher educational attainment has not been shown to attenuate cognitive impairment in brain tumour patients, younger age and having a frontal tumour were associated with better performance on speed, executive and working memory measures (Kaleita et al., 2004). In a recent study, we retrospectively examined the effects of years of education and literacy attainment measured by the NART IQ on the cognitive performance of patients with unilateral prefrontal lesions due to stroke or brain tumour (MacPherson et al., 2017). NART IQ predicted executive and naming performance but not fluid intelligence, processing speed, verbal short-term memory or perceptual abilities. Importantly, however, our study showed that the effects of education and/or NART IQ on our cognitive measures did not interact with lesion severity, arguing against a frontal theory of CR effect i.e., the effect of lesion severity on cognitive impairment was not altered by either CR proxy in our frontal patients. One limitation of our previous study was that data from patients with non-frontal lesions were not available. This would have allowed us to directly compare whether the degree of variance accounted for by CR is reduced in frontal patients when compared to non-frontal patients.

In the current study, we examined the effect of CR, as measured using NART IQ, on the cognitive performance of a large sample of patients with focal, unilateral frontal or non-frontal brain regions due to stroke or tumour. Our aim was to compare the influence of lesion location (frontal vs. non-frontal) on cognitive performance in order to determine whether CR

differentially safeguards against focal neuropathology according to lesion location. If the frontal theory of CR is to be supported, NART IQ will account for less variance on the cognitive tests in frontal patients compared to non-frontal patients.

MATERIALS AND METHODS

Participants

The patient database within the Neuropsychology Department at the National Hospital for Neurology and Neurosurgery was retrospectively examined for patients with frontal or non-frontal lesions who could be included in the study. Patients were identified as having a unilateral lesion confined to either the frontal or non-frontal brain regions due to a stroke or a brain tumour by a neurologist on the basis of clinical MRI scans (or CT scans where MRI was unavailable). Lesions were localised by operation site in the case of surgical patients or by gross lesion characterisation in the nonsurgical patients. Tumour grade was confirmed by histopathological studies following resection or biopsy and patients had undergone tumour resection prior to neuropsychological assessment. Exclusion criteria were (i) age \geq 80 years at the time of testing, (ii) current or previous psychiatric disorders, (iii) previous neurological disorders including previous stroke or tumours, (iv) presence of metastatic tumours, (v) previous chemotherapy, (vi) gross visual, perceptual, language or motor impairment, (vii) previous head trauma, (viii) history of excessive alcohol or drug use, (ix) no MRI or CT scan results available, (x) no or limited neuropsychological data available, (xi) a score below the 5th percentile on a test of general intelligence (Wechsler Adult Intelligence Scale-III, WAIS-III; Wechsler, 1997, Wechsler Adult Intelligence Scale-R, 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 \geq 25th percentile on the National Adult Reading Test (NART, Nelson, 1982) to ensure their English abilities were able to cope with task demands. One hundred and sixty-

six frontal patients were included in the study: stroke, N=53; high-grade tumour, N=27; low-grade tumour, N=37; and meningioma, N=49. Some clinical and cognitive aspects of these patients have been previously reported (MacPherson et al., 2010, 2016, 2017; Robinson et al., 2012, 2015; Murphy et al., 2013; Cipolotti et al., 2015a). Ninety-one non-frontal patients were included in the study: stroke, N=30; high-grade tumour, N=19; low-grade tumour, N=22; and meningioma, N=20. See Table 1 for the lesion localisation of the non-frontal patients. Data from 136 healthy controls (HC) were also included (see below). The study was approved by the National Hospital for Neurology and Neurosurgery and the Institute of Neurology Joint Research Ethics Committee (UK), all procedures were in accordance with the Declaration of Helsinki, and all participants provided informed written consent.

- Insert Table 1 around here -

Cognitive Investigation

All patients had previously undertaken a single neuropsychological assessment in the Neuropsychology Department of the National Hospital for Neurology and Neurosurgery which involved the administration of established neuropsychological tests assessing executive abilities (phonemic fluency S – number of words produced; Tombaugh et al., 1999), intelligence (WAIS-III – full Scale IQ; Wechsler, 1997), speed of information processing (Trail Making Test Part-A, Trail-A – number of seconds to complete; Reitan, 1992) and naming (Graded Naming Test, GNT – number of pictures correctly named; McKenna & Warrington, 1983). Test administration was conducted in accordance with the procedures outlined in test manuals. The neuropsychological tests selected and administered during the assessment were at the discretion of the different clinical neuropsychologists; hence, data for the various tests were not available for all participants. A pairwise deletion method was used with no

substitutions made to the dependent variables. Fewer neuropsychological tests were considered compared to MacPherson et al. (2017) to allow the inclusion of more patients. Of the 166 frontal patients, the individuals who had data for each cognitive measure were as follows: executive function: N=147; intellectual abilities: N=82; speed of information processing: N=77; and naming: N=156. For the 91 non-frontal patients, the individuals who had data for each cognitive measure were as follows: executive function: N=56; intellectual abilities: N=71; speed of information processing: N=20; and naming: N=57. For the 136 HC, the individuals who had data for each cognitive measure were: executive function: N=43; intellectual abilities: N=0; speed of information processing: N=81; and naming: N=131.

Cognitive Reserve Proxy

Literacy attainment was included as our proxy of CR. A test of single word reading was adopted (e.g., Scarmeas et al., 2006; Stern et al., 2008). This was based on NART IQ, which has a split-half reliability coefficient of 0.93, inter-rater reliability of 0.96-0.98 and test-retest reliability of 0.98 (O'Carroll, 1987; Crawford et al., 1989a; Schlosser & Ivison, 1989b). In terms of validity, the NART loads highly (0.85) on g, the general factor of intelligence from the WAIS (Crawford et al., 1989b).

Statistical Analysis

The statistical analyses were carried out using R version 3.6.0. The effect of our CR proxy on performance on the cognitive measures was examined by fitting separate multiple linear regression models for each measure using R function 'lm'. In the first step of the analysis, age (step 1) was entered as a continuous predictor variable. In step 2, lesion group was entered as a categorical predictor variable with 3 levels (frontal, non-frontal and HC). Here, two dichotomous dummy coded variables were created and directly entered into the model: frontal

versus HC and non-frontal versus HC. In the case of WAIS-III where HC data were not available, there was only one dichotomous variable comparing frontal versus non-frontal. The third step involved NART IQ (step 3) being entered as a predictor variable to examine the contributions of our CR proxy to cognitive performance, in addition to any effect of age and lesion group. In the final step, the interaction term between lesion group (dichotomous variables: frontal versus HC and non-frontal versus HC) and NART IQ (step 4) was added to the model to determine whether any association between the CR proxy and cognitive performance differed across groups.

As the assumption of normality of the residuals was violated, log10 transformations of the dependent variables were carried out prior to conducting the regression analyses. For all models, the contribution and significance of each predictor was estimated at each step and exponentiated betas values are reported. As multiple regression models were fitted for each neuropsychological test (i.e., fluency, WAIS Full-Scale IQ, Trail Making Test Part-A and GNT), the p-value was Bonferroni corrected ($0.05/4 = 0.0125$). For each linear regression model, the variance inflation factor (VIF) was used to examine multi-collinearity. In all instances, the VIF was below 2, indicating that there were not high intercorrelations among predictor variables. Missing values for our dependent variables were not imputed as the imputation process is not thought to provide additional information, and may introduce additional error (von Hippel, 2007).

RESULTS

Table 2 demonstrates the means and standard deviations for the demographic and neuropsychological performance of the frontal, non-frontal and HC groups.

- Insert Table 2 around here -

Prior to running the regression models, we demonstrated that the different aetiology subgroups (i.e., stroke, high-grade glioma, low-grade glioma and meningioma) did not significantly differ in their performance on the neuropsychological tests (except our low-grade glioma frontal patients who were significantly faster on Trail Making Test Part-A than the other frontal aetiology groups; see Tables 1 and 2 in the online Supplemental Materials). Of note, this group of patients was also significantly younger. On the whole, it appears methodologically justifiable to group together patients with different aetiologies for the purpose of cognitive analyses (for similar conclusions in frontal patients see Cipolotti et al., 2015a). Table 3 shows the results of the multiple linear regression models testing for the effect of NART IQ on each cognitive test.

Letter Fluency 'S' Test. In the case of letter fluency, NART IQ significantly predicted performance where the higher the NART IQ, the more words were produced. Lesion group also significantly contributed to the model fit with frontal patients producing significantly fewer words than HC. Non-frontal patients did not significantly differ from HC. Age also contributed to the fit of the model, where younger individuals produced more words. The final model explained 17% of the variance ($F(4,241) = 11.93, p < .0001$). The interaction between lesion group and NART IQ did not significantly contribute to participants' fluency performance.

WAIS-III Full-Scale IQ. NART IQ significantly contributed to performance on WAIS IQ, where the higher the NART IQ, the higher the WAIS-III full-scale IQ. Lesion group also independently predicted performance with the frontal patients having significantly higher full-scale IQ scores than the non-frontal group. Age did not contribute to the model. NART IQ and lesion group accounted for 39% of the variance on WAIS IQ ($F(3,149) = 32.15, p < .0001$). The interaction term between lesion group and NART IQ did not significantly contribute to the models.

Trail Making Part-A (Trail-A). Age significantly predicted Trail-A performance, accounting for 17% of the variance ($F(1,176) = 35.53, p < .0001$), where the younger the patient, the faster the performance. Entering lesion group or NART IQ did not significantly improve the fit of the model.

Graded Naming Test (GNT). Again, NART IQ was a significant predictor of performance, where the higher the NART IQ, the higher the GNT performance. Lesion group also significantly contributed to performance on the GNT where the frontal patients performed significantly more poorly than HC. Non-frontal patients did not significantly differ from HC. Age did not contribute to the model at any stage. NART IQ accounted for 36% of the variance on the GNT ($F(4,339) = 47.21, p < .0001$). Again, lesion group did not contribute to the model as an interaction term with NART IQ.

- Insert Table 3 around here -

DISCUSSION

In this retrospective study, we examined the influence of literacy attainment based on NART IQ on neuropsychological test performance in a large sample of patients with unilateral frontal or non-frontal lesions and HCs. Our analyses revealed that our frontal group performed significantly poorer than HCs on the executive (i.e., fluency) and naming tests (i.e., GNT). In contrast, our frontal patients were not significantly slower than HCs on the test of processing speed and had significantly higher full-scale IQs compared to our non-frontal group. The reduced fluency performance in our frontal patients supports previous patient studies (e.g., Milner, 1964; Perret, 1974; Robinson et al., 2012; Stuss et al., 1998; Troyer et al., 1998; see Henry & Crawford, 2004; Cipolotti et al., 2020).

In terms of the contribution of NART IQ on neuropsychological test performance, after adjusting for age and lesion group (frontal and non-frontal versus HC), NART IQ predicted performance on fluency, intelligence and naming. Our previous work involving only frontal patients has demonstrated that NART IQ predicts executive and naming performance (MacPherson et al., 2017). Here we provide further support for the predictive nature of the NART in terms of cognition following frontal and non-frontal lesions. Importantly, however, the influence of NART IQ on neuropsychological test performance does not differ across lesion groups suggesting that the frontal lobes do not play a role in mediating CR effect.

Of course, it remains possible that there may be specific frontal subregions associated with CR and cognitive performance and only damage to these specific subregions may hinder any benefits of CR. For example, regions such as the superior, middle and inferior frontal gyri, as well as frontal lobe-associated networks (e.g., left anterior intraparietal sulcus; Bastin et al., 2012) have been associated with CR (for a review see Anthony & Lin, 2017) and damage to these specific regions may prevent compensation from CR after brain injury. In addition, we did not consider parameters such as white matter intensities (WMH) and cortical atrophy in our patients. Patients with high CR estimates have been found to have greater quantities of WMH than patients with low CR estimates and yet may perform equally well or better on cognitive tasks (e.g., Brickman et al., 2011; Jokinen et al., 2016; Murray et al., 2011). However, given the heterogeneous neuroimaging data that were available for our retrospective study through clinical scans, as well as our sample size, it was not possible to investigate focal damage to specific frontal or non-frontal subregions. Yet, the major strength of our retrospective study is that it follows on and supports our previous findings examining the effects of CR proxies in frontal patients due to stroke or tumour (MacPherson et al., 2017). To our knowledge, the current study is the first to examine the influence of a CR proxy on the performance of a large

group of patients with unilateral frontal and non-frontal lesions across different cognitive measures.

It should also be pointed out that patients with more severe brain lesions were not included in our study due to their inability to cope with the demands of our cognitive tests. Therefore, we cannot rule out the possibility that more severe frontal lesions may not safeguard against focal neuropathology and moderate cognitive impairment across these various cognitive measures. In our previous work (MacPherson et al., 2017), we observed that the patients who were not included in our retrospective study tended to have extensive frontal lobe lesions. Moreover, those frontal patients with high lesion severity performed significantly more poorly on fluency and speed of processing tasks than frontal patients with low lesion severity, despite being matched on education and NART IQ. Future prospective studies examining the effects of CR in patients with focal frontal and non-frontal lesions are needed to examine the role of lesion severity on cognition.

Age independently predicted performance on fluency and Trail-Making Part-A but not WAIS-III and GNT. This is in line with our previous work demonstrating that age and NART IQ influence performance on a range of cognitive measures in a smaller group of frontal patients, some of whom have also participated in the current study (Cipolotti et al., 2015b; MacPherson et al., 2017). However, age did not predict our frontal and non-frontal patients' intellectual abilities. As our data are age-scaled, these findings suggest that there is not a further effect of age on our patient population over-and-above the adjustments made using normative data.

Our analyses indicate that performance on Trail-Making Test Part-A is predicted only by age. Yet, we acknowledge that our sample size for the Trail-Making Test Part-A is small, particularly for the non-frontal patients (i.e., non-frontal = 20, frontal = 77 and HC = 81), so caution should be taken when concluding that NART is selectively unrelated to processing

speed. Nonetheless, in our MacPherson et al. (2017) study involving frontal patients only, we similarly reported that age was the only significant contributor to the fit of the Trail Making Part-A model and education and NART IQ made no significant contributions to the model at any stage. Future prospective work is needed to examine further the relationship between CR proxies and speed of processing, as well as other aspects of cognition.

Following a common practice in neuropsychology, we mixed different aetiologies in our patients' samples to obtain a large enough group. Previously we have reported that there was not a significant difference between 100 frontal patients with four different types of aetiology (i.e., stroke, high-grade glioma, low-grade glioma and meningioma) on four frontal executive tasks (Cipolotti et al., 2015a). Critically, it remained unknown if the effects of strokes and tumours were roughly equivalent when affecting the non-frontal cortex. In our Supplementary Materials, we document for the first time that the cognitive performance in our non-frontal patients was not affected by variability in lesion aetiology. Our subgroups of non-frontal patients with stroke, high- or low-grade tumour or meningioma did not differ in their performance on tests of frontal executive (fluency), intelligence (WAIS-III), processing speed (Trail-A) or naming (GNT). Similarly, our patients with frontal lesions due to stroke, high- or low-grade tumour or meningioma did not differ in their performance on the neuropsychological tests except our test of processing speed (Trail Making Test Part-A) where the low-grade tumour patients were significantly faster than the other frontal aetiology groups. This is perhaps not surprising given our low-grade glioma frontal group were significantly younger than the other aetiology subgroups and individuals start to show age-related decline in processing speed as early as their 30s (Baxendale, 2011). Previous research examining cognition in glioma patients has also reported that processing speed is less impaired in low-grade compared to high-grade glioma, although this impairment was not specific to frontal lesions (Dehcordi et al., 2013; Miotto et al., 2011; van Kessel et al., 2019). While grouping patients with different

aetiologies is likely to suffer from potential confounds, it remains necessary to obtain large groups of patients to investigate cognitive impairments (for similar approaches see Aridan et al., 2019; Aron et al., 2004; Gläscher et al., 2012; Roca et al., 2010; Stamenova et al., 2017; Stuss et al., 2005; Thompson–Schill et al., 1998; Urbanski et al., 2016). Some other studies favour the use of a single aetiology (e.g., Baldo et al., 2006; Campanella et al., 2016; Sperber & Karnath, 2017; Varjačić et al., 2018). However, there is no consensus in the field of neuropsychology regarding what is the best approach to adopt. As a minimum, we have attempted to demonstrate that certain aetiologies do not result in more severe impairments than others (see also Cipolotti et al., 2015a).

In summary, our CR analyses suggest that age and NART IQ provide protective effects of focal brain pathology in patients with lesions due to stroke or brain tumour. However, importantly, the relationship between NART IQ and cognitive performance following focal brain damage does not differ between frontal and non-frontal lesions. Therefore, environmental factors shape resilience to cognitive decline in both patients who have experienced focal frontal or non-frontal lesions. Future work involving prospective studies should be conducted to examine further the complex relationship between CR, age and frontal/non-frontal regions when attempting to understand impairments and recovery on cognitive tasks. CR may influence the degree of recovery post-stroke or brain tumour, which is critical for our understanding of the recovery process. CR may also be a predictive factor of the efficacy of neuropsychological rehabilitation training in individuals who have experienced focal brain damage, regardless of the brain area damaged.

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Table 1. Distribution of the non-frontal patients according to lesion area and hemisphere.

| Area | Hemisphere | <i>N</i> |
|---------------------------|------------|----------|
| Cerebellum | Left | 1 |
| Occipital | Left | 5 |
| | Right | 2 |
| Parietal | Left | 10 |
| | Right | 8 |
| Parieto-occipital | Left | 5 |
| | Right | 4 |
| Temporal | Left | 18 |
| | Right | 22 |
| Temporo-occipital | Left | 2 |
| | Right | 3 |
| Temporo-parietal | Left | 5 |
| | Right | 5 |
| Temporo-parieto-occipital | Right | 1 |

Table 2. Means and standard deviations (SD) for the demographic and neuropsychological performance of the frontal, non-frontal and HC groups.

| Groups | Frontal group (<i>N</i> = 166) | Non-frontal group (<i>N</i> = 91) | HC group (<i>N</i> = 136) |
|---|---------------------------------------|--|----------------------------------|
| Gender (M/F) | 93/73 | 58/33 | 76/60 |
| Age | 49.33 (14.54) | 49.73 (13.74) | 46.18 (15.62) |
| Education (years) | 13.73 (2.92) | 13.93 (3.15) | 13.62 (2.74) |
| Time between damage and assessment (months) | 23.74 (48.11) | 19.78 (56.98) | - |
| NART IQ | 109.93 (10.31) | 109.85 (10.34) | 109.82 (7.56) |
| Fluency | 13.60 (6.25) | 14.25 (5.11) | 17.02 (5.01) |
| WAIS-III | 106.24 (16.64) | 100.20 (13.78) | - |
| Trail-A | 34.70 (11.26) | 33.00 (10.51) | 31.71 (10.22) |
| GNT | 20.96 (4.24) | 22.33 (3.99) | 22.16 (3.55) |

Note: HC = healthy controls; WAIS-III = Wechsler Adult Intelligence Scale-III; Trail-A =

Trail Making Test Part-A; GNT = Graded Naming Test

Table 3. Regression models for the four cognitive tests.

| Test | Variable | Step 1 (Age) | | | | Step 2 (Lesion group) | | | | Step 3 (NART IQ) | | | | Step 4 (Lesion group x NART IQ) | | | |
|--|-----------|-----------------|--------------|------------------|-------|--------------------------|--------------|------------------|-------|---------------------|---------------|------------------|-------|---------------------------------------|--------------|------------------|-------|
| | | β | SE | p | R^2 | B | SE | p | R^2 | β | SE | p | R^2 | β | SE | p | R^2 |
| Fluency ($N = 246$) | Age | 1.00 | 0.001 | <.001 | 0.05 | 1.00 | 0.001 | <.001 | 0.10 | 1.00 | 0.001 | <.0001 | 0.17 | 1.00 | 0.001 | <.0001 | 0.17 |
| | F | | | | | 0.87 | 0.04 | <.001 | | 0.88 | 0.04 | <.001 | | 0.83 | 0.07 | <.001 | |
| | NF | | | | | 0.91 | 0.05 | =.04 | | 0.92 | 0.05 | =.07 | | 0.89 | 0.07 | =.12 | |
| | NART | | | | | | | | | 1.01 | 0.001 | <.0001 | | 1.00 | 0.01 | =.55 | |
| | F x NART | | | | | | | | | | | | | 1.00 | 0.01 | =.34 | |
| | NF x NART | | | | | | | | | | | | | 1.00 | 0.01 | =.67 | |
| WAIS-III ^a ($N = 153$) | Age | 1.00 | 0.0004 | =.59 | 0.002 | 1.00 | 0.0004 | =.55 | 0.04 | 1.00 | 0.0003 | =.04 | 0.39 | 1.00 | 0.0003 | =.04 | 0.40 |
| | NF | | | | | 0.98 | 0.01 | =.02 | | 0.98 | 0.01 | <.01 | | 0.99 | 0.01 | =.42 | |
| | NART | | | | | | | | | 1.00 | 0.0004 | <.0001 | | 1.00 | 0.001 | <.0001 | |
| | NF x NART | | | | | | | | | | | | | 1.00 | 0.001 | =.11 | |
| Trail-A ($N = 178$) | Age | 1.00 | 0.001 | <.0001 | 0.17 | 1.00 | 0.001 | <.0001 | 0.19 | 1.00 | 0.001 | <.0001 | 0.20 | 1.00 | 0.001 | <.0001 | 0.21 |
| | F | | | | | 1.05 | 0.021 | =.02 | | 1.05 | 0.02 | =.02 | | 1.03 | 0.03 | =.25 | |
| | NF | | | | | 1.01 | 0.033 | =.75 | | 1.01 | 0.03 | =.72 | | 0.98 | 0.05 | =.60 | |
| | NART | | | | | | | | | 1.00 | 0.001 | =.18 | | 1.00 | 0.002 | =.11 | |
| | F x NART | | | | | | | | | | | | | 1.00 | 0.002 | =.40 | |
| | NF x NART | | | | | | | | | | | | | 1.00 | 0.004 | =.26 | |
| GNT ($N = 344$) | Age | 1.00 | 0.0003 | =.08 | 0.009 | 1.00 | 0.0003 | =.05 | 0.04 | 1.00 | 0.0003 | =.70 | 0.36 | 1.00 | 0.0003 | =.60 | 0.37 |
| | F | | | | | 0.97 | 0.01 | <.01 | | 0.98 | 0.008 | <.01 | | 0.97 | 0.01 | <.01 | |
| | NF | | | | | 1.00 | 0.013 | =.98 | | 0.99 | 0.011 | =.41 | | 1.01 | 0.02 | =.62 | |
| | NART | | | | | | | | | 1.01 | 0.0004 | <.0001 | | 1.01 | 0.001 | <.0001 | |
| | F x NART | | | | | | | | | | | | | 1.00 | 0.001 | =.36 | |
| | NF x NART | | | | | | | | | | | | | 1.00 | 0.001 | =.26 | |

Note. F = frontal patients; NF = non-frontal patients; group factor baseline level = healthy controls; ^agroup factor baseline level = frontal

patients; WAIS = Wechsler Adult Intelligence Scale; Trail-A = Trail Making Test Part-A; GNT = Graded Naming Test.

Exponentiated betas are reported. Bonferroni adjusted p-value < 0.0125.

Supplementary Table 1. Demographic information for the four frontal and non-frontal aetiology subgroups: Means and standard deviations (SD)

| | Stroke (<i>N</i> = 83) | High-grade glioma (<i>N</i> = 46) | Low-grade glioma (<i>N</i> = 59) | Meningioma (<i>N</i> = 69) | <i>p</i> value |
|-----------------------------------|-------------------------------|--|---|--------------------------------|----------------|
| Gender (M/F) | | | | | |
| Frontal | 27/26 | 21/6 | 23/14 | 22/27 | < .05 |
| Non-frontal | 19/11 | 14/5 | 13/9 | 12/8 | = .77 |
| Age in years | | | | | |
| Frontal | 51.77 ^a (15.19) | 43.56 ^b (12.10) | 38.00 ^b (9.41) | 58.43 (11.04) | < .001 |
| Non-frontal | 53.10 (13.11) | 49.89 (11.40) | 44.95 (16.17) | 49.75 (13.23) | = .23 |
| Education in years | | | | | |
| Frontal | 13.15 (2.67) | 14.81 (2.57) | 14.11 (3.04) | 13.39 (3.11) | = .07 |
| Non-frontal | 13.70 (3.50) | 14.16 (3.00) | 13.68 (2.91) | 14.32 (3.13) | = .89 |
| NART IQ | | | | | |
| Frontal | 108.79 (10.29) | 109.11 (10.10) | 112.70 (9.71) | 109.18 (10.80) | = .29 |
| Non-frontal | 111.20 (10.68) | 113.00 (9.65) | 106.00 (9.46) | 109.05 (10.71) | = .14 |
| Time since damage (months) | | | | | |
| Frontal | 22.06 (49.28) | 6.48 (9.57) | 10.82 (21.02) | 47.39 (65.95) | < .01 |
| Non-frontal | 25.13 (78.46) | 7.30 (10.46) | 21.43 (66.99) | 21.98 (28.96) | = .75 |

Note: ^a < meningioma; ^b < stroke and meningioma.

Supplementary Table 2. Neuropsychological test performance for the four frontal and non-frontal aetiology subgroups: Means and standard deviations (SD)

| | Stroke | High-grade glioma | Low-grade glioma | Meningioma | <i>p</i> value |
|---------------------------|--|--|--|-----------------------------------|----------------|
| Fluency (total no. words) | | | | | |
| Frontal ^a | 12.82 (6.03) <i>N</i> =38 | 12.74 (6.47) <i>N</i> =27 | 16.67 (5.60) <i>N</i> =36 | 12.35 (6.17) <i>N</i> =46 | = .11 |
| Non-frontal | 13.95 (4.99) <i>N</i> =21 | 14.73 (6.45) <i>N</i> =11 | 14.31 (6.32) <i>N</i> =13 | 14.27 (1.95) <i>N</i> =11 | = .95 |
| WAIS-III Full-Scale IQ | | | | | |
| Frontal ^a | 101.82 (15.84) <i>N</i> =33 | 101.36 (15.27) <i>N</i> =11 | 112.80 (18.70) <i>N</i> =20 | 110.06 (14.14) <i>N</i> =18 | = .08 |
| Non-frontal | 102.17 (14.80) <i>N</i> =24 | 98.19 (15.26) <i>N</i> =16 | 102.59 (11.34) <i>N</i> =17 | 96.21 (13.07) <i>N</i> =14 | = .48 |
| Trail-A (in seconds) | | | | | |
| Frontal ^a | 37.27 ^b (8.93) <i>N</i> =23 | 31.74 ^c (6.67) <i>N</i> =16 | 26.32 ^c (9.29) <i>N</i> =22 | 45.51 (10.61) <i>N</i> =16 | < .001 |
| Non-frontal | 25.50 (10.61) <i>N</i> =2 | 36.40 (11.01) <i>N</i> =5 | 29.93 (10.95) <i>N</i> =8 | 37.53 (8.85) <i>N</i> =5 | = .39 |
| GNT (out of 30) | | | | | |
| Frontal ^a | 19.68 (4.60) <i>N</i> =47 | 21.33 (4.09) <i>N</i> =27 | 22.06 (3.30) <i>N</i> =35 | 21.21 (4.37) <i>N</i> =47 | = .12 |
| Non-frontal | 22.63 (3.86) <i>N</i> =19 | 21.77 (4.13) <i>N</i> =13 | 22.29 (3.91) <i>N</i> =14 | 22.55 (4.63) <i>N</i> =11 | = .94 |

Note: ^a controlling for age and time since lesion onset; ^b > low grade glioma; ^c < meningioma; WAIS-III = Wechsler Adult Intelligence Scale-III; Trail-A = Trail Making Test Part-A; GNT = Graded Naming Test.