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

Journal:	*Journal of the International Neuropsychological S*
Manuscript ID	JINS-19-Reg-GS-255.R1
Manuscript Type:	Regular Research
Date Submitted by the Author:	17-Jan-2020
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MeSH Keywords:	Cognitive Reserve, Frontal Lesions, Neuropsychological tests, Age, Aetiology, Nonfrontal Lesions
Topic Areas:	Executive Abilities/Function, Fluency (verbal, nonverbal), Frontal Lobes, Literacy, Elderly/Aging

Response to Reviewers

Manuscript number: JINS-19-Reg-GS-255

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Reviewer 1:

1. It may be of substantial help to the reader if the authors would reconsider their writing in the last two paragraphs of the Introduction section. In addition to expressing their goals with greater overall clarity, numbering the goals and following them up with hypotheses would be very helpful. Subsequently, the authors could more clearly rely on these goals when describing details of the study in the Analysis section, presenting their results in the Results section, and interpreting these results in the Discussion.

Author response: We are grateful for the Reviewer's comment that made us realise that the last two paragraphs of our Introduction were not as clear as we would have hoped. We have now rewritten these two paragraphs and removed our discussion on aetiology from the main manuscript in an attempt to improve its clarity and focus. The aetiology analyses are now in our Supplementary Material (see our response to Reviewer #2, point 23). Furthermore, in response to Reviewer #2, point 24, our manuscript now only focuses on NART IQ as our CR proxy and the effect of NART IQ on the cognitive performance of frontal and non-frontal patients. We hope that our manuscript's hypotheses and analyses are now clearer for the reader.

"If the prefrontal cortex is responsible for 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."

2. Your thesis sentence of the 2nd paragraph indicates age- and disease-related brain changes. Elaborate on "recovery". This study deviates from conventional examination of cognitive reserve, whereby studies focus on describing dementia-related neurodegeneration rather than post-stroke recovery. How do the two areas converge and diverge? This should also be part of your discussion.

Author response: In the second paragraph, where we mention recovery, we now clarify that we are referring to cognitive improvement after brain injury rather than neurodegenerative conditions:

"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)."

Later in our Introduction on page 4, we now briefly mention potential differences between neurodegenerative conditions and post-brain injury in terms of CR:

"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."

3. Table 1 is not very informative. Consider adding this information to the text of the manuscript. Alternatively, the information on page 8 (under the heading cognitive investigation) where you outline the samples for the specific tests could be included to enhance the table.

Author response: In line with the Reviewer's suggestion, we have now removed this information from Table 1 and included it in the main text of the Cognitive Investigation section instead.

4. Provide reliability and validity information about the NART IQ measure.

Author response: We have now provided reliability and validity information for the NART:

"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)."

5. Organize Statistical Analysis section along your study aims and use some system (numbering?) to help the reader follow what tests go with what aim.

Author response: As already discussed above, we have now removed our aetiology analysis from the main manuscript and focused our manuscript on the CR analyses. We now only briefly mention the aetiology analysis at the beginning of our Results section to direct readers to our Supplementary Materials.

6. The Results section is very difficult to follow. Please use your aims the same way as suggested for the Analysis section in item 4. Also, why is first section of Results focused on non-frontal patients only?

Table 2 has a column named "Group", which just adds to the confusion. Is there a mistake? The non-frontal group is not even mentioned in Table 2.

Author response: We have moved our aetiology Tables 2 and 3 to the Supplementary Materials and include both frontal and non-frontal patients in our analyses rather than only considering non-frontal patients. Here we find that no aetiology groups differ in their cognitive performance except our frontal low-grade glioma group is significantly faster than our other frontal aetiology groups. At the beginning of our Results section, we state:

"*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).*"

Later in our Discussion section, we state:

"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).

We have also removed the name "Group" from the column in Table 2 as we agree it was confusing.

7. When indicating that a Bonferroni correction for the multiple regressions was used for four tests, make clear which four tests you are talking about. There appears to be more than four tests and five different models. Also, point the reader to our final model on which you base your conclusions.

Author response: We apologise for the lack of clarity here. We have now stated that we are referring to the four neuropsychological tests when we correct for multiple analyses:

"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)."

Minor Points

8. Make sure to define your acronyms at their first mention (i.e., AD)

Author response: We thank the Reviewer for pointing this out and have now ensured we define our acronyms when they are first presented.

9. Please provide your rationale for choosing the Kruskal-Wallis test over the ANOVA.

Author response: We have now removed our aetiology analysis from the main manuscript in response to the Reviewers' comments and therefore, this point is no longer relevant.

10. In your results, under the section "Demographic and Neuropsychological Results in Non-Frontal Patients," you say no effect of age, education, or NART. No effect on what DV?

Author response: Again, as we have now removed our aetiology analysis from the main manuscript, this point is no longer relevant.

11. For the trail making results, you say that age is the only significant predictor. However, in the table, group F is significant in Step 5a ($p = .01$, which is less than your Bonferroni-corrected p of .0125). Please address.

Author response: In the Trail Making regression models, the models that included additional predictors, over and above age, did not significantly differ from the model that included age only. This is why we state age is the only significant predictor. However, as we have now removed education from the analyses at the request of Reviewer #2, this is no longer an issue.

12. For the GNT results, you say that age did not contribute at any stage, but the table shows that in step 3 and 5a that age was a significant predictor. Please address.

Author response: As above, while some models have significant predictors, the addition of these predictors does not significantly improve the fit of the models. However, as we have now removed education from the analyses at the request of Reviewer #2, again this is no longer an issue.

13. On page 13, it is unclear what you mean by "chronicity" when discussing figure 1.

Author response: Apologies, this is a typo and we have now removed "chronicity" from the sentence discussing Figure 1.

14. In your discussion, when you are discussing the frontal etiologies, you state vascular—do you mean stroke? Be consistent in naming terms.

Author response: We have now used the term "stroke" throughout to be consistent in the terms we use.

15. When speaking about the non-frontal lesions, it would be helpful to include whether the locations of the lesions were the same or different (more information about the localization of the lesions would be appreciated).

Author response: We have now included a table that provides the lesion localisation of our non-frontal patients (see Table 1).

16. In the discussion, paragraph 3 on page 14, the sentence "Our previous work has also provided evidence of mild nominal deficits associated with the GNT in unselected frontal lesion groups" is unclear.

Author response: We realise this sentence is not clear and have now removed it from our Discussion section.

17. In the discussion on page 15, you conclude that the frontal lobes do not play a mediating role in the CR effect. This conclusion may be beyond your current investigation since you do not include patients with more severe frontal lesions or specify localization of the frontal lesions (except that they are frontal). Thus, the frontal lobes could mediate the role of CR, but it is not evident in your current sample. Consider rewording the strength of this conclusion or including your limitation information (on page 16 "it is also possible that there are specific frontal subregions…") closer to this statement.

Author response: We thank the Reviewer for this suggestion and have now moved our limitation information re the possibility of specific frontal subregions being associated with CR to the next paragraph to make it clear that our conclusion that the frontal lobes do not play a mediating role in the CR effect is based on our current sample of frontal patients.

18. In the discussion on page 16, the paragraph beginning "it is also possible that…" the second sentence through the Murray et al., 2011 reference needs to be reviewed. This section is unclear.

Author response: We realise now that the paragraph was not clear and have attempted to clarify the points we were attempting to make:

"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).”

19. Table 2: Include that you are looking only at the non-frontal lesion group in title. Also correct the formatting to include “Note.” You also seem to be missing a word in the last sentence of the note. Include your sample size.

Author response: We have now moved this table to our Supplementary Materials (see Tables 1 and 2) and include both our frontal and non-frontal groups. We have also added “Note” to the bottom and include our sample size.

20. Table 3: Correct formatting to include “Note.” Need sample size.

Author response: This is now Table 2 and we have both “Note” and our sample size.

21. Table 4: Hard to follow the table with the current formatting. It also does not fit well on the page when printing. Consider dropping the word “group” from the variable name. This will save space and help with the formatting. Additional APA formatting notes: specific notes are typically superscript letters instead of asterisks, N is italicized, correct spacing on the sample size equation. Also, please justify why you started at step 3 instead of step 1 for the multiple regression models. Consider adding R2 values to the table.

Author response: We thank the Reviewer for highlighting our APA formatting errors and have now made the necessary changes. We have also now included all steps in our models and added the R^2 values to the table and removed Figure 1.

22. Figure 1: The stars are off. Explain why you did not include Step 5 from your regression models. Also, make sure you are consistent in your naming (state the test you included instead of the cognitive process, or include the test in addition to the cognitive process). Significance of IVs is unclear in terms of changes in variance

explained. May be clearer to add R2 to the Table instead of having this in the figure. Also in the caption you note that the significant predictors for the final models are indicated, but they are not. Again, using "predictors" in this study is questionable.

Author response: As suggested by the Reviewer, we have now removed Figure 1 and added the R^2 values to Table 3 instead.

Reviewer 2:

23. The authors address a number of aims that are seemingly unrelated, which makes for a confusing read. The title and introduction emphasize cognitive reserve as the focus of investigation, which primes the reader for a study on this topic. However, a good deal of the results and discussion sections of the manuscript are devoted to the unrelated topic of lesion etiology influences on cognitive performance. I don't know why this topic is examined in such detail in this manuscript. Simply covarying for etiology (as the authors rightly do) seems sufficient.

Author response: In response to both Reviewer #1 and #2, we have now removed our aetiology analysis from the main manuscript to focus our readers on our CR analyses. We now only briefly mention these analyses at the beginning of our Results section to direct readers to our Supplementary Materials and to justify our inclusion of non-frontal patients with varying aetiologies.

24. The authors choose to examine both education and literacy as proxies for cognitive reserve, and do not really provide any rationale for examining both proxies. They contrast the relative influences of these two variables on cognitive performance in their sample, and find literacy to be the stronger predictor of cognitive performance. Unfortunately, I think the generalizability of this finding is very limited, due both to the small sample size and the fact that the range of educational attainment in the study sample is very narrow. Education influences adult cognition via multiple pathways, and I don't think there is enough heterogeneity of educational attainment in this sample to do this topic justice. It would be preferable to examine a composite variable or to simply examine literacy, rather than attempting to make statements about the relative influence of these two complexly interwoven variables. Of note, there is a rich literature devoted to characterizing the pathways linking education, literacy, and other early-life exposures with cognitive performance in later life, but none of this makes its way into the manuscript.

Author response: In response to the Reviewer's point re the lack of variability in our patients' educational attainment, we have now removed our analyses with education as a CR proxy and focus only

on literacy attainment, as measured using NART IQ. We also now include some references to early-life exposures and later life cognition in our first paragraph:

"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)."

25. This manuscript could be reformatted as a brief report demonstrating no differential effect of education or literacy on cognitive performance as a function of frontal vs. non-frontal lesion. In its current form it is too meandering and includes superfluous analyses that are not well-suited to the study sample.

Author response: We have now removed the education CR analyses and aetiology from our manuscript. We hope this means that the Reviewer finds the manuscript more focused and less meandering.

Reviewer 3:

26. Please review the description of participants in the abstract (i.e., believe you intended to write "91 patients with focal, unilateral NON-frontal lesions" rather than "frontal lesions").

Author response: Thank you to the Reviewer for pointing out this typo. We have now corrected our abstract to read, "...91 patients with focal, unilateral non-frontal lesions..."

27. Make sure when you write comparative statements (i.e., more, less, worse, better, higher, lower) that they are all written in the intended direction.

Author response: We have attempted to write our comparative statements in the intended direction.

28. In the introduction and/or discussion, it might worth noting any relevant imaging research conducted on cognitive reserve and what those relevant findings might be.

Author response: We have now included a paragraph that discusses the results of neuroimaging studies examining CR:

"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)."

29. What are the clinical implications of these findings? Please discuss the value of this work.

Author response: We have now included clinical implications of our findings and future work:

"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."

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

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Word count: 4,665

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; Perneczky 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 ≥ 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 ≥ 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 significant 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.

ACKNOWLEDGEMENTS

This project was funded by Wellcome Trust (grant numbers 066763, 089231/A/09/Z) and supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre. The authors declare no conflicts of interest.

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

Area	Hemisphere	*N*
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
Temoporo-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 ($N = 166$)	Non-frontal group ($N = 91$)	HC group ($N = 136$)
Gender (M/F)	93/73	58/33	76/60
Age	49.33	49.73	46.18
	(14.54)	(13.74)	(15.62)
Education (years)	13.73	13.93	13.62
	(2.92)	(3.15)	(2.74)
Time between damage and assessment (months)	23.74	19.78	-
	(48.11)	(56.98)	
NART IQ	109.93	109.85	109.82
	(10.31)	(10.34)	(7.56)
Fluency	13.60	14.25	17.02
	(6.25)	(5.11)	(5.01)
WAIS-III	106.24	100.20	-
	(16.64)	(13.78)	
Trail-A	34.70	33.00	31.71
	(11.26)	(10.51)	(10.22)
GNT	20.96	22.33	22.16
	(4.24)	(3.99)	(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***	***R²***	***β***	**SE**	***p***	***R²***	***β***	**SE**	***p***	***R²***	***β***	**SE**	***p***	***R²***
Fluency	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
(*N* = 246)	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]	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
(*N* = 153)	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	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
(*N* = 178)	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	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
(*N* = 344)	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; [a]group 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 ($N = 83$)	High-grade glioma ($N = 46$)	Low-grade glioma ($N = 59$)	Meningioma ($N = 69$)	p 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]	43.56[b]	38.00[b]	58.43	< .001
	(15.19)	(12.10)	(9.41)	(11.04)	
Non-frontal	53.10	49.89	44.95	49.75	= .23
	(13.11)	(11.40)	(16.17)	(13.23)	
Education in years					
Frontal	13.15	14.81	14.11	13.39	= .07
	(2.67)	(2.57)	(3.04)	(3.11)	
Non-frontal	13.70	14.16	13.68	14.32	= .89
	(3.50)	(3.00)	(2.91)	(3.13)	
NART IQ					
Frontal	108.79	109.11	112.70	109.18	= .29
	(10.29)	(10.10)	(9.71)	(10.80)	
Non-frontal	111.20	113.00	106.00	109.05	= .14
	(10.68)	(9.65)	(9.46)	(10.71)	
Time since damage (months)					
Frontal	22.06	6.48	10.82	47.39	< .01
	(49.28)	(9.57)	(21.02)	(65.95)	
Non-frontal	25.13	7.30	21.43	21.98	= .75
	(78.46)	(10.46)	(66.99)	(28.96)	

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