

Global efficiency of structural networks mediates cognitive control in Mild Cognitive Impairment

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Provisional

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2 **Cognitive Impairment**

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1 **Abstract**

2 Background: Cognitive control has been linked to both the microstructure of individual
3 tracts and the structure of whole-brain networks, but their relative contributions in health
4 and disease remain unclear.

5 Objective: To determine the contribution of both localised white matter tract damage and
6 disruption of global network architecture to cognitive control, in older age and Mild
7 Cognitive Impairment (MCI).

8 Methods: 25 patients with MCI and 20 age, sex and intelligence-matched healthy
9 volunteers were investigated with 3 Tesla structural magnetic resonance imaging (MRI).
10 Cognitive control and episodic memory were evaluated with established tests. Structural
11 network graphs were constructed from diffusion MRI-based whole-brain tractography.
12 Their global measures were calculated using graph theory. Regression models utilized
13 both global network metrics and microstructure of specific connections, known to be
14 critical for each domain, to predict cognitive scores.

15 Results: Global efficiency and the mean clustering coefficient of networks were reduced
16 in MCI. Cognitive control was associated with global network topology. Episodic
17 memory, in contrast, correlated with individual temporal tracts only. Relationships
18 between cognitive control and network topology were attenuated by addition of single
19 tract measures to regression models, consistent with a partial mediation effect. The
20 mediation effect was stronger in MCI than healthy volunteers, explaining 23-36% of the
21 effect of cingulum microstructure on cognitive control performance. Network clustering
22 was a significant mediator in the relationship between tract microstructure and cognitive
23 control in both groups.

24 Conclusions: The status of critical connections and large-scale network topology are both
25 important for maintenance of cognitive control in MCI. Mediation via large-scale
26 networks is more important in patients with MCI than healthy volunteers. This effect is
27 domain-specific, and true for cognitive control but not for episodic memory.
28 Interventions to improve cognitive control will need to address both dysfunction of local
29 circuitry and global network architecture to be maximally effective.

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31

32

33 **Keywords**

34 cognitive aging, cognitive control, mild cognitive impairment, tractography,

35 neuroimaging, diffusion MRI, networks

1. Introduction

Cognitive or executive control describes the marshalling of cognitive resources in the face of complex or competing demands (Shenhav et al., 2013). Impairment of control is an important feature of dementia (Royall et al., 1998) and is associated with changes in brain structure. We have previously shown that alterations in a single portion of the anterior cingulum bundle predict variation of cognitive control in healthy older people (Metzler-Baddeley et al., 2012a). This observation fits with a key role for the dorsal anterior cingulate cortex (Shenhav et al., 2013). However, this is only one node of a widely distributed network that is activated by control tasks (Cole and Schneider, 2007). Alterations in brain structure occur at multiple levels with aging and early neurodegeneration. An alternative viewpoint, therefore, is that performance might depend on emergent properties of the whole network rather than any single tract. The relationship between alterations at the level of tracts and whole networks, and their relative contribution to cognitive performance in aging and neurologic disease, are not known.

Cognitive control and episodic memory have traditionally been associated with structures in the prefrontal cortex and medial temporal lobe, respectively (Gläscher et al., 2012; Alexander et al., 2007). This anatomical parcellation of function extends to key white matter connections. Cognitive control is exquisitely sensitive to microstructural differences in subsets of pathways within the cingulum bundle, including those likely to terminate in the dorsal anterior cingulate cortex (Metzler-Baddeley et al., 2012a). It is not, however, associated with variations in fornix microstructure, the principal correlate of verbal recall (Metzler-Baddeley et al., 2011). In Mild Cognitive Impairment (MCI), the prodromal stage of Alzheimer's disease, microstructure is compromised in the fornix and other temporal tracts and residual memory performance remains dependent on temporal lobe connections (Metzler-Baddeley et al., 2012b). Performance, therefore, has been linked with relative specificity to microstructure of white matter connections within relevant networks.

Graph theory provides a means to derive properties of the brain's global 'connectome', such as measures of efficiency of network structure and clustering of network nodes (Rubinov and Sporns, 2012). *Global efficiency* is inversely related to topological distance between nodes and is typically interpreted as a measure of the capacity for parallel information transfer and integrated processing (Bullmore and Sporns, 2012). The *clustering coefficient* is a measure more weighted to the local environment of each node, as it quantifies the extent to which neighbouring nodes are connected to each other (Bullmore and Sporns, 2009). Reduced efficiency of network structure has been demonstrated in Alzheimer's disease and linked to performance in both memory and executive tasks (Lo et al., 2010; Reijmer et al., 2013). In MCI, similar alterations in structural network topology have been observed, though findings at this early stage of neurodegeneration are less consistent (Bai et al., 2012; Shu et al., 2012).

Previous neuroimaging studies have generally not considered both 'local' (nodes and

1 connections) and ‘global’ (network topology) measures together. To date, diffusion MRI
2 studies have tended to focus either on detailed tract reconstructions or whole-brain
3 approaches. It remains unclear how microstructural changes in single tracts relate to
4 global network topology, and how important such a pathway of effect might be in
5 cognitive function and dysfunction. This is a particularly relevant question for cognitive
6 control. The cingulate cortex and its connections harbour critical functional
7 specialisation, but the cingulum also provides a pathway of communication across large-
8 scale networks whose topology might also relate to cognition.

9
10 The interplay between local tracts and global network properties – and the spatial scale of
11 organisation that is most relevant to performance – have important implications for
12 treatment. Treatments based on noninvasive stimulation could target specific local
13 alterations in function, or the restoration of more widespread patterns of network
14 structure and function. For example, transcranial magnetic stimulation has been shown to
15 normalise functional connectivity in depression (Liston et al., 2014), and transcranial
16 direct current stimulation also influences resting-state networks (Peña-Gómez et al.,
17 2012). This study combined investigation of critical tracts with global properties of
18 structural networks. We determined whether network topology was altered in MCI and
19 whether such alterations were an independent factor in cognitive performance. Mediation
20 analyses were used to test the hypothesis that relationships between tract microstructure
21 and cognition were mediated by alterations in global network topology.

22 23 24 **2. Material and Methods**

25 26 **2.1 Participants**

27 25 patients with MCI were recruited from the Cardiff Memory Clinic. Standardised
28 assessment included clinical history, ascertainment of vascular risk status, neurological
29 examination, basic haematology and biochemistry investigations, neuroimaging with CT
30 or MRI and cognitive screening with the Addenbrooke’s Cognitive Examination (Mioshi
31 et al., 2006). Diagnosis of MCI was based on established current criteria (Albert et al.,
32 2011). Objective memory impairment was confirmed by a score of > 1.5 SDs below age-
33 matched controls on either the Addenbrooke’s verbal memory subscore or the visual
34 memory test from the Repeatable Battery for the Assessment of Neurological Status. All
35 patients had a Mini-Mental State Examination score of ≥ 24 (mean 26, SD 1.7) and a
36 Clinical Dementia Rating of 0.5. Seven patients had additional evidence of executive
37 dysfunction (multidomain MCI), others had pure amnesic MCI. Consecutive patients,
38 who were eligible and willing to take part, were recruited and assessed by a single
39 neurologist (MJO).

40
41 The 20 healthy control participants were drawn from 46 individuals between the ages of
42 53 and 93 years, recruited for an aging study (Metzler-Baddeley et al., 2011). Among the
43 46 elderly participants, one withdrew and another did not complete the study due to ill
44 health. One participant was excluded because of subsequent diagnosis of Parkinson’s
45 disease. Structural MRI scans (fluid-attenuated inversion recovery and T1-weighted)
46 were inspected for overt pathology: three participants were excluded because of extensive

1 white matter hyperintensities suggestive of significant cerebral small vessel disease
2 (Fazekas grade 3) (Fazekas et al., 1993), and one participant was excluded due to severe
3 motion artifact. From remaining 39 subjects, a matched control group was sampled. The
4 control sample were matched for age and premorbid IQ using data from the National
5 Adult Reading Test-Revised (NART-R), an accepted measure of premorbid IQ. Age and
6 NART-R only were used to select this group and to prevent bias, selection was performed
7 blind to cognitive, clinical and MRI data. Participants older than 65 years (the MCI group
8 were all over 65) and with a verbal IQ not exceeding 2 SDs above the average patient IQ
9 in the NART-R provided a matched sample of 20 healthy control participants.

10
11 Exclusion criteria for both groups were: a history of neurological disease or mental
12 disorders (clinical disorders or acute medical conditions/physical disorders, as defined by
13 DSM-IV-TR), including past history of moderate to severe head injury, prior or current
14 drug or alcohol abuse, previous large-artery stroke or cerebral hemorrhage, known
15 cervical, peripheral or coronary artery disease, structural heart disease or heart failure,
16 and contraindications to MRI. Anxiety or antidepressant use was not an exclusion
17 criterion, unless an individual met criteria for major depression. No patient with MCI met
18 diagnostic criteria or had characteristic clinical features to suggest other degenerative
19 disorders. An additional exclusion criterion for healthy participants was the past or
20 current presence of subjective memory symptoms.

21
22 Ethical approval for the study was provided by the South East Wales Research Ethics
23 Committee. All participants provided informed consent in accordance with the
24 Declaration of Helsinki.

25 26 **2.2 Cognitive assessment**

27 Neuropsychological assessment was performed over two 1.5-hour testing sessions.
28 Cognitive control was assessed with tasks that required the maintenance of a task set
29 under speeded response conditions: attention switching was examined using alternation
30 between letters and digits with a Verbal Trails Test. The Stroop Color-Word test was
31 used to assess the suppression of response incongruent information (Trenerry et al.,
32 1989). Verbal generation and fluency were measured with the verbal fluency tests from
33 the D-KEFS for letters F, A and S and for the categories of animals and boys' names.
34 Motor planning skills based on spatial rules were assessed with the Tower of London test
35 from the Delis and Kaplan Executive Function System battery (D-KEFS). The Digit
36 Symbol Substitution test from the WAIS-III provided a measure of focused attention and
37 psychomotor performance.

38
39 Free recall was assessed with the Free and Cued Selective Reminding Test (Grober et al.,
40 1997). Additionally, the face recognition test from the Camden Recognition Memory
41 Test (CRMT) was performed.

42 43 **2.3 MRI acquisition**

44 Diffusion-weighted MRI data were acquired using a 3T GE HDx MRI system (General
45 Electric) with a twice-refocused spin-echo echo planar imaging sequence, providing
46 whole oblique axial (parallel to the commissural plane) brain coverage (60 slices, 2.4 mm

1 thickness, field of view 23 cm, acquisition matrix 96 x 96). Acquisition was peripherally
2 gated to the cardiac cycle. TE (echo delay time) was 87 ms and parallel imaging (array
3 spatial sensitivity encoding (ASSET) factor 2) was used. The b-value was 1,200 s/mm².
4 Data were acquired with diffusion encoded along 30 isotropically distributed directions
5 and 3 non-diffusion-weighted scans, according to an optimised gradient vector scheme
6 (Jones et al., 1999). Acquisition time was approximately 13 min.

7
8 T₁-weighted structural MRI data were acquired using a 3D fast spoiled gradient recalled
9 (FSPGR) echo sequence (matrix of 256 × 256 × 176, field of view of 256 × 256 × 176
10 mm, resulting in isotropic 1 mm resolution). The timing parameters were TR/TE/TI =
11 7.9/3.0/450ms, and the flip angle was 20°.

12 13 **2.4 Image processing and tractography**

14 The acquired diffusion-weighted images were corrected for distortion and motion
15 artefacts with reorientation of encoding vectors (Leemans and Jones, 2009) and
16 modulation of the signal intensity by the Jacobian determinant of the transformation
17 (Jones and Cercignani, 2010). The free-water elimination approach was used to correct
18 for atrophy-related partial volume effects due to CSF contamination (Pasternak et al.,
19 2009; Berlot et al, 2014).

20
21 Whole-brain tractography was performed using ExploreDTI (www.exploreDTI.com) and
22 a diffusion tensor model using every voxel as a seed point. A deterministic tracking
23 algorithm estimated the principal diffusion orientation at each seed point and propagated
24 in 0.5 mm steps along this direction. The fibre orientation was then estimated at the new
25 location and tracking moved a further 0.5 mm along the direction that subtended the
26 minimum change of principal direction. A streamline was traced until fractional
27 anisotropy fell below 0.15 or the change in direction exceeded 60°.

28
29 Three-dimensional reconstructions of the cingulum and of temporal association tracts
30 were derived. Detailed reconstruction algorithms and linked reproducibility data,
31 showing good reproducibility, have been described previously (Metzler-Baddeley et al.,
32 2011, 2012a, 2012b).

33
34 Whole brain volume, normalised for head size, was estimated with SIENAX (Smith et
35 al., 2002), part of FSL (FMRIB Software Library, <http://www.fmrib.ox.ac.uk/fsl/>, Version
36 5.0). White matter lesions were segmented and their total volume quantified using a
37 multispectral image-processing tool, MCMxxxVI (Hernandez et al., 2010).

38 39 **2.5 Network construction and graph theory-based analysis**

40 Whole-brain tract reconstructions were transformed into Montreal Neurological Institute
41 (MNI) space within ExploreDTI, using a non-rigid transformation utilizing B-splines.
42 Grey matter was then parcellated into 90 cortical and subcortical regions, 45 for each
43 hemisphere, using the automated anatomical labeling (AAL) atlas (Figure 1). Each region
44 was used to define a node of a network graph. Edges were defined by tractography
45 streamlines connecting any pair of nodes. An edge was defined as present between two
46 nodes if a streamline was reconstructed with start and end points in each. Networks were

1 weighted by the number of reconstructed streamlines.

2
3 Network metrics were computed using Brain Connectivity Toolbox
4 (<https://sites.google.com/site/bctnet>) (Rubinov and Sporns, 2010). We investigated
5 measures of global and local network architecture: global efficiency, mean clustering
6 coefficient and small-worldness.

8 **2.6 Statistical analysis**

9 Global efficiency, clustering coefficient and small-worldness were compared between
10 MCI and control groups using unpaired t-tests. Associations with cognitive scores were
11 computed in each group separately using Pearson's product-moment correlation
12 coefficients. Bonferroni correction for multiple comparisons was applied based on the
13 number of network measures. Cognitive measures tend to be strongly correlated with
14 each other and in these circumstances Bonferroni correction is vastly over-conservative,
15 so correction was not applied for the number of cognitive measures. Partial correlation
16 coefficients were calculated accounting for potential confounding variables: age, gender,
17 education (in years), total brain volume and total white matter lesion volume.

18
19 Linear regression models were constructed for Category Fluency and Digit Symbol
20 Substitution task performance to investigate mediation effects. Measures of tract
21 microstructure that were used were based on previously determined associations between
22 Category Fluency and Digit Symbol Substitution, and the microstructure of cingulum
23 segments: left anterior fractional anisotropy in controls, and left posterior mean
24 diffusivity in MCI. These associations were identified in a previous analysis of the same
25 dataset (based on diffusion MRI but not including network graph or graph theory
26 measures), detailed in Metzler-Baddeley et al. (2012a). Separate models were constructed
27 that included: i) tract microstructure alone; or ii) both tract microstructure and a single
28 network measure. Thus, the relationships between tract microstructure and cognition, and
29 network topology and cognition were established, and the influence of tract
30 microstructure on cognition while controlling for network topology was assessed. The
31 mediation effect was assessed as a decrease in the value of the standardised regression
32 coefficients (β) for the association between cingulum microstructure and cognition after
33 inclusion of a network measure in the model. Estimates of direct and indirect causal
34 effects were obtained from the models using the non-parametric bootstrapping approach,
35 and the proportion mediated by the network measure was estimated (Imai et al., 2010).
36 This approach allowed measurement of a partial mediation effect and was not aimed at
37 showing full mediation (where inclusion of a mediator leads to a measured association
38 between two factors falling to zero). To test specificity of the investigated relationships
39 for cognitive control, a similar analysis was performed for episodic memory: parallel
40 regression models were constructed with free recall as the dependent variable and fornix
41 tissue volume fraction as the relevant single-tract measure (Metzler-Baddeley et al.,
42 2012b).

43
44 Structural equation modelling was performed within the statistical software package R
45 (www.r-project.org), using an approach analogous to previous studies (Lawrence et al.,
46 2014; Knopman et al., 2015). Tract and network measures were tested for interaction in

1 each model. No significant interaction was found; therefore interaction terms were not
2 included in final models. For terms in all models, variance inflation factors indicated no
3 significant multicollinearity (variance inflation factors < 3).

6 **3. Results**

8 **3.1 Group comparisons**

9 Demographic, cognitive and general MRI measures for the groups are provided in Table
10 1. Structural networks of both healthy older adults and patients with MCI exhibited
11 small-world topology. There was no difference in small-worldness between groups. In
12 contrast, both global efficiency and mean clustering coefficient were reduced in MCI. On
13 the basis of group differences, global efficiency and mean clustering coefficient were
14 taken forward to analysis of relationships with cognition (leading to Bonferroni-corrected
15 significance equivalent to uncorrected $p < .025$).

17 **3.2 Relationship between network metrics and cognitive scores**

18 In MCI, both global efficiency and mean clustering coefficient were associated with
19 cognitive control (Tables 2 and 3). In contrast, there were no relationships between global
20 network measures and episodic memory performance. Measures of network topology
21 were not correlated with cognitive scores in control participants.

23 **3.3 Cognitive control, global network properties and individual tract structure**

24 In MCI, the inclusion of global network properties led to an attenuation of the
25 relationship between single tract microstructure and cognition (Tables 4 and 5). For
26 Category Fluency, both left posterior cingulum microstructure and mean clustering
27 coefficient were significant independent predictors (Table 5).

29 Figure 2 displays path diagrams of the mediation analysis. The magnitudes of mediation
30 effects are summarized in Figure 3. The proportion of the effect of cingulum
31 microstructure on cognitive scores, mediated by global efficiency, varied from 22-35%
32 (Figure 3). In patients, the mediation effect was strongest for the relationship between left
33 posterior cingulum and Category Fluency, 31% of which was explained by global
34 efficiency ($p = .12$) and 36% by mean clustering coefficient ($p = .02$). Mean clustering
35 coefficient was also a significant partial mediator of the link between left anterior
36 cingulum and Category Fluency in controls (19% of variance due to mediation effect, $p =$
37 $.04$). Mediation effects of network topology were not demonstrated for episodic memory
38 and the association between fornix structure and free recall, in either of the two groups
39 (Table 6, Figure 3).

41 **4. Discussion**

43 MCI is often considered a prodrome of dementia. We showed previously that
44 microstructure is altered in white matter tracts in MCI and that alterations in specific
45 tracts relate to specific aspects of the cognitive deficit. The present analysis demonstrates
46 that global properties of the structural connectome are also altered. Patients with MCI had

1 reduced global efficiency and mean clustering coefficient, in comparison with matched
2 controls. While whole-brain network measures were not related to episodic memory,
3 measures of network efficiency and clustering were related to cognitive control in MCI.
4 This was the case despite the fact that episodic memory deficits were the most consistent,
5 indeed defining feature of the MCI group. Episodic memory impairment was a
6 prerequisite for the diagnosis while only seven patients with MCI displayed additional
7 executive deficits. This result suggests that global networks are perturbed in MCI, but are
8 not critical to the core deficit in episodic memory, which relates to damage within the
9 relatively narrow and circumscribed extended hippocampal network.

10
11 A relationship between network efficiency and executive function has been described in
12 Alzheimer's disease (Reijmer et al., 2013), but also in other brain disorders such as
13 traumatic brain injury (Caeyenberghs et al., 2012), small-vessel disease (Lawrence et al.,
14 2014) and cerebral amyloid angiopathy (Reijmer et al., 2015). In patients with small-
15 vessel disease and cerebral amyloid angiopathy, network measures were related only to
16 executive function, but not memory performance. However, in these diseases episodic
17 memory deficits are mild or absent, so this dissociation might have been explained by a
18 lack of variance in memory scores. In the present study, conversely, episodic memory
19 was impaired to a greater extent, and more consistently, than cognitive control. This
20 dissociation therefore is more likely to reflect the functional anatomy of cognitive control
21 and episodic memory in the brain and the dependence of cognitive control on a more
22 diffuse network. Further, when correlations were controlled for the volume of white
23 matter lesions, as well as other potential confounders, the pattern of associations
24 remained consistent, and in some cases became stronger, indicating that small vessel
25 disease did not account for the associations observed in this study. Mediation analyses
26 suggested that the relationship between cingulum microstructure and cognitive control
27 was partly mediated by global network topology, while no such link was observed for the
28 relationship between fornix structure and episodic memory. These findings further
29 underline a qualitatively different relationship between tracts and cognitive function for
30 cognitive control and episodic memory.

31
32 One intriguing parallel to the pattern of results is that pathological processes also vary in
33 whether they target local structures or more global infrastructure. For example, amyloid
34 and tau pathologies have strong local predilections, at least early in the course of disease.
35 Microvascular disease, on the other hand, leads to diffuse alterations in white matter
36 microstructure so, potentially, it could have a general effect on network efficiency
37 (Lawrence et al., 2014). One strength of the approach taken is that it provides a way to
38 understand how coexistent pathologies could interact. For example, localised
39 neurodegeneration and network-wide effects of diffuse microvascular disease could act
40 synergistically to impair cognitive or executive control.

41
42 However, the contrasting relationships of network topology to episodic memory and
43 cognitive control might also be related to methodology used. One possibility is that
44 episodic memory depends on a network that more heavily involves subcortical structures
45 and connections, particularly in the diencephalon, and that in turn topology of these
46 networks is not strongly represented in whole-brain network metrics, constructed using

1 current methods. Parcellation of nodes might be more effective for networks that involve
2 multiple neocortical regions, such as those involved in cognitive control, than for
3 networks with fine-grained subcortical anatomy. The AAL atlas used, as well as
4 alternative parcellation techniques, do not include the mammillary bodies, for example,
5 which are crucial structures within the extended hippocampal network involved in
6 episodic memory.

7
8 The pattern of results suggests that damage to a tract such as the cingulum can degrade
9 cognitive performance through two distinct roles of this tract – as a conduit for
10 communication of specific information within a dedicated network for cognitive control,
11 and as a more generic “backbone” for communication across global brain networks.
12 Previous work has shown that hub regions such as the anterior and posterior cingulate
13 cortices, and their connections, might be important not only because they harbour critical
14 functional specialisations but also because they mediate connectivity across the structural
15 network more broadly including, for example, in the case of the posterior cingulate
16 cortex, tuning network metastability (Leech and Sharp, 2014).

17
18 A limitation of this study, common to studies based on tractography, is the risk of false
19 positive and false negative connections. Weighting of network edges by the total number
20 of reconstructed streamlines should reduce the impact of anatomically spurious edges as,
21 in general, only a few outlier streamlines will run between regions that do not have a true
22 connection. The choice of method for weighting edges is a controversial aspect of the
23 application of graph theory to structural networks. Number of streamlines was used to
24 offer consistency with previous studies and to avoid using microstructural measures
25 known to be abnormal in MCI, but the effect of different weighting approaches has not
26 been investigated in detail. Cognitive control is multifaceted and a number of measures
27 provide overlapping insights into these processes. The Bonferroni method is highly over-
28 conservative in the presence of multiple inter-correlated measures. Correction was
29 therefore applied for number of network measures but not for number of cognitive
30 measures, so that the risk of false positive correlations may not be completely eliminated
31 in the regression analyses. Similarly, a large number of mediation models could have
32 been constructed based on different measures. To minimise the risk of mediation
33 emerging by chance, we selected the two measures most consistently associated with
34 cognition in regression analysis (Tables 2 and 3). In addition, a limitation of the
35 mediation analysis performed is that we cannot make definite conclusions on the
36 direction of the effect. Even though it seems less biologically plausible, our results do not
37 exclude the possibility of cingulum microstructure mediating the effect of network
38 topology on cognition.

39
40 Further insight into the dynamics of the relationship between ‘local’ and ‘global’ disease-
41 related alterations could be gained by observing our population in a longitudinal setting,
42 or additionally including a group of patients with more severe cognitive impairment. The
43 current study does not extend to brain function, inferred from functional MRI data. It is
44 possible that the topology of structural networks will not be entirely reflected by
45 functional networks, which differ in being dynamic over short time scales. Finally, the
46 interplay between ‘local’ and ‘global’ structural and functional changes might be of

1 interest beyond cognitive function. Functional variation within the cingulate cortex and
2 the large-scale networks might be related to the expression of specific clinical
3 phenotypes, rather than disease-related alterations, such as the occurrence of
4 hyperarousal, anxiety or hallucinations in neurodegenerative disorders (Franciotti et al.,
5 2015). A similar approach could be used to test this hypothesis in Alzheimer's disease
6 and other neurodegenerative disorders.

7
8 Potential treatments such as transcranial magnetic stimulation or direct current
9 stimulation have largely been thought of in terms of localised effects on function.
10 However, a number of studies show that treatment delivered locally can have effects on
11 global network topology and dynamics (Polanía et al., 2011; Shafi et al., 2014). In
12 principle, these wider effects could also be harnessed to restore network function. Our
13 results suggest that for some functions – such as cognitive control – the ideal strategy
14 may involve targeting both local and global alterations in brain structure and function.

15 16 **5. Author Contributions**

17
18 RB contributed to study conception, data analysis, statistical analysis, writing and editing
19 the manuscript. CMB contributed to study conception, data collection, writing and editing
20 the manuscript. MAI contributed to data analysis, statistical analysis, writing and editing
21 the manuscript. DKJ contributed to data collection, data analysis, writing and editing the
22 manuscript. MOS contributed to study conception and design, data collection, data
23 analysis, writing and editing the manuscript.

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35 36 **7. Conflict of Interest Statement**

37
38 The authors declare that the research was conducted in the absence of any commercial or
39 financial relationships that could be construed as a potential conflict of interest.

40 41 42 **8. References**

43
44 Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., *et al.*
45 (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease:
46 recommendations from the National Institute on Aging-Alzheimer's

1 Association workgroups on diagnostic guidelines for Alzheimer's disease.
2 *Alzheimers. Dement.* 7, 270-279.

3 Alexander, M.P., Stuss, D.T., Picton, T., Shallice, T., Gillingham, S. (2007). Regional
4 frontal injuries cause distinct impairments in cognitive control. *Neurology.* 68, 1515-
5 1523.

6 Bai, F., Shu, N., Yuan, Y., Shi, Y., Yu, H., Wu, D., *et al.* (2012). Topologically
7 convergent and divergent structural connectivity patterns between patients with
8 remitted geriatric depression and amnesic mild cognitive impairment. *J. Neurosci.*
9 32(12), 4307-4318.

10 Berlot, R., Metzler-Baddeley, C., Jones, D.K., O'Sullivan, M.J. (2014) CSF
11 contamination contributes to apparent microstructural alterations in mild cognitive
12 impairment. *Neuroimage.* 92, 27-35.

13 Bullmore, E., Sporns, O. (2009). Complex brain networks: graph theoretical analysis of
14 structural and functional systems. *Nat. Rev. Neurosci.* 10, 186-198.

15 Bullmore, E., Sporns, O. (2012). The economy of brain network organization. *Nat. Rev.*
16 *Neurosci.* 13, 336-349.

17 Caeyenberghs, K., Leemans, A., Leunissen, I., Gooijers, J., Michiels, K., Sunaert, S., *e*
18 *tal.* (2012). Altered structural networks and executive deficits in traumatic brain
19 injury patients. *Brain. Struct. Funct.* 219, 193-209.

20 Cole, M.W., and Schneider, W. (2007). The cognitive control network: integrated cortical
21 regions with dissociable functions. *Neuroimage.* 37, 343-360.

22 Fazekas, F., Kleinert, R., Offenbacher, H., Schmidt, R., Kleinert, G., Payer, F., *et al.*
23 (1993). Pathological correlates of incidental MRI white matter signal hyperintensities.
24 *Neurology.* 43, 1683-1689.

25 Franciotti, R., Delli Pizzi, S., Perfetti, B., Tartaro, A., Bonanni, L., Thomas, A., *et al.*
26 Default mode network links to visual hallucinations: A comparison between
27 Parkinson's disease and multiple system atrophy. *Mov. Disord.* 30(9): 1237-1247.

28 Gläscher, J., Adolphs, R., Damasio, H., Bechara, A., Rudrauf, D., Calamia, M., *et al.*
29 (2012). Lesion mapping of cognitive control and value-based decision making in the
30 prefrontal cortex. *Proc. Natl. Acad. Sci. USA.* 109, 14681-14686.

31 Grober, E., Merling, A., Heimlich, T., Lipton, R.B. (1997). Free and cued selective
32 reminding and selective reminding in the elderly. *J. Clin. Exp. Neuropsychol.* 19, 643-
33 654.

34 Hernandez, M.C.V., Ferguson, K.J., Chappell, F.M., Wardlaw, J.M. (2010). New
35 multispectral MRI data fusion technique for white matter lesion segmentation:
36 method and comparison with thresholding in FLAIR images. *Eur. Radiol.* 20, 1684-
37 1691.

38 Imai, K., Keele, L., Tingley, D. (2010). A general approach to causal mediation analysis.
39 *Psychol. Methods.* 15, 309-334.

40 Jones, D.K., Horsfield, M.A., Simmons, A. (1999). Optimal strategies for measuring
41 diffusion in anisotropic systems by magnetic resonance imaging. *Magn. Reson. Med.*
42 42, 515-525.

43 Jones, D.K., and Cercignani, M. (2010). Twenty-five pitfalls in the analysis of diffusion
44 MRI data. *NMR Biomed.* 23, 803-820.

45 Knopman, D.S., Griswold, M.E., Lirecte, S.T., Gottesman, R.F., Kantarci, K., Sharrett,
46 A.R., *e tal.* (2015). Vascular imaging abnormalities and cognition: mediation by

1 cortical volume in nondemented individuals: atherosclerosis risk in communities –
2 neurocognitive study. *Stroke*. 46, 433-440.

3 Lawrence, A.J., Chung, A.W., Morris, R.G., Markus, H.S., Barrick, T.R. (2014).
4 Structural network efficiency is associated with cognitive impairment in small-vessel
5 disease. *Neurology*. 83, 304-311.

6 Leech, R., and Sharp, D.J. (2014). The role of the posterior cingulate cortex in cognition
7 and disease. *Brain*. 137, 12-32.

8 Leemans, A., and Jones, D.K. (2009). The B-matrix must be rotated when correcting for
9 subject motion in DTI data. *Magn. Reson. Med*. 61,1336-1349.

10 Liston, C., Chen, A.C., Zebley, B.D., Drysdale, A.T., Gordon, R., Leuchter, B., *et al.*
11 (2014). Default mode network mechanisms of transcranial magnetic stimulation in
12 depression. *Biol. Psychiatry*. 76(7), 517-526.

13 Lo, C.Y., Wang, P.N., Chou, K.H., Wang, J., He, Y., Lin, C.P. (2010). Diffusion tensor
14 tractography reveals abnormal topological organization in structural cortical networks
15 in Alzheimer's disease. *J. Neurosci*. 30(50), 16876-16885.

16 Metzler-Baddeley, C., Jones, D.K., Belaroussi, B., Aggleton J.P., O'Sullivan M.J. (2011).
17 Frontotemporal connections in episodic memory and aging: a diffusion MRI
18 tractography study. *J. Neurosci*. 31(37), 13236-13245.

19 Metzler-Baddeley, C., Jones, D.K., Steventon, J., Westacott, L., Aggleton, J.P.,
20 O'Sullivan, M.J. (2012a). Cingulum microstructure predicts cognitive control in older
21 age and mild cognitive impairment. *J. Neurosci*. 32(49), 17612-17619.

22 Metzler-Baddeley, C., Hunt, S., Jones, D.K., Leemans, A., Aggleton, J.P., O'Sullivan,
23 M.J. (2012b). Temporal association tracts and the breakdown of episodic memory in
24 mild cognitive impairment. *Neurology*. 79(23), 2233-2240.

25 Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., Hodghes, J.R. (2006). The
26 Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery
27 for dementia screening. *Int. J. Geriatr. Psychiatry*. 21, 1078-1085.

28 Pasternak, O., Sochen, N., Gur, Y., Intrator, N., Assaf, Y. (2009). Free water elimination
29 and mapping from diffusion MRI. *Magn. Reson. Med*. 62, 717-730.

30 Peña-Gómez, C., Sala-Lonch, R., Junqué, C., Clemente, I.C., Vidal, D., Bargalló, N., *et*
31 *al.* (2012). Modulation of large-scale brain networks by transcranial direct current
32 stimulation evidenced by resting-state functional MRI. *Brain. Stimul*. 5(3), 252-263.

33 Polanía, R., Paulus, W., Antal, A., Nitsche, M.A. (2011). Introducing graph theory to
34 track for neuroplastic alterations in the resting human brain: a transcranial direct
35 current stimulation study. *Neuroimage*. 54, 2287-2296.

36 Reijmer, Y.D., Leemans, A., Caeyenberghs, K., Heringa, S.M., Koek, H.L., Biessels,
37 G.J., *et al.* (2013). Disruption of cerebral networks and cognitive impairment in
38 Alzheimer disease. *Neurology*. 80, 1370-1377.

39 Reijmer, Y.D., Fotiadis, P., Martinez-Ramirez, S., Salat, D.H., Schultz, A., Shoamanesh,
40 A., *et al.* (2015). Structural network alterations and neurological dysfunction in
41 cerebral amyloid angiopathy. *Brain*. 138, 179-188.

42 Royall, D.R., Cabello, M., Polk, M.J. (1998). Executive dyscontrol: an important factor
43 affecting the level of care received by older retirees. *J. Am. Geriatr. Soc*. 46, 1519-
44 1524.

45 Rubinov, M., and Sporns, O. (2010). Complex network measures of brain connectivity:
46 uses and interpretations. *Neuroimage*. 52(3), 1059-1069.

- 1 Shafi, M.M., Brandon Westover, M., Oberman, L., Cash, S.S., Pascual-Leone, A. (2014).
2 Modulation of EEG functional connectivity networks in subjects undergoing repetitive
3 transcranial magnetic stimulation. *Brain. Topogr.* 27, 172-191.
- 4 Shenhav, A., Botvinick, M.M., Cohen, J.D. (2013). The expected value of control: an
5 integrative theory of anterior cingulate cortex function. *Neuron.* 79, 217-240.
- 6 Shu, N., Liang, Y., Li, H., Zhang, J., Li, X., Wang, L., *et al.* (2012). Disrupted
7 topological organization in white matter structural networks in amnesic mild
8 cognitive impairment: relationship to subtype. *Radiology.* 265, 518-527.
- 9 Smith, S.M., Zhang, Y., Jenkinson, M., Chen, J., Matthews, P.M., Federico. A., *et al.*
10 (2002). Accurate, robust and automated longitudinal and cross-sectional brain change
11 analysis. *Neuroimage.* 17, 479-489.
- 12 Trenerry, M., Crosson, B., DeBoe, J., Leber, W. (1989). *Stroop Neuropsychological*
13 *Screening Test manual.* Odessa, FL: Psychological Assessment Resourcer (PAR).
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1 **9. Figure Legends**

2
3 **Figure 1. Overview of methods.** After preprocessing each diffusion tensor imaging
4 dataset (A), whole-brain tractography was performed (B). Cingulum segments of interest
5 were reconstructed (C) – left anterior in healthy elderly (yellow), left posterior in patients
6 with mild cognitive impairment (red). Whole-brain tractograms were coregistered to the
7 automated anatomical labeling atlas template (D), consisting of 90 regions corresponding
8 to nodes of the network. The number of reconstructed streamlines between any two
9 regions of the template was used to weight network edges, resulting in a 90 x 90
10 weighted adjacency matrix (E). Measures of network topology were computed for
11 individual brain networks (F). Tract and network measures were assessed as predictors of
12 cognitive control performance (G). Age, gender, educational attainment, brain volume
13 and volume of white matter hyperintensities were used as covariates.

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16 **Figure 2. Mediation models for the effect of global efficiency and mean clustering**
17 **coefficient in healthy volunteers (A) and patients with MCI (B).** Diagrams present
18 standardised regression coefficients for each path in the model; coefficients after the slash
19 show path values adjusted for the mediation effect. Coefficients in bold correspond to
20 significant associations ($p < .05$). p values stand for significance of combined models.
21 The proportion of the effect of tract microstructure (fractional anisotropy – FA; mean
22 diffusivity – MD; tissue volume fraction – f), mediated by the measure of network
23 topology, is displayed as percentage with parenthetical p value, corresponding to the
24 significance of the mediation effect.

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27 **Figure 3. Proportion of the effect explained by mediation.** The proportion of the effect
28 of cingulum microstructure on cognition mediated by network topology in controls and
29 patients with MCI. Error bars correspond to the interquartile range.

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1 **Table 1. Demographic data and group comparison of cognitive scores, MRI**
 2 **measures and measures of network topology.** Data are shown as mean (SD). A cube
 3 root transform was applied to white matter lesion volume. Significant differences ($p <$
 4 $.05$) are highlighted in bold.
 5 MCI – Mild Cognitive Impairment; NART-R – National Adult Reading Test-Revised;
 6 FCSRT – Free and Cued Selective Reminding Test; CRMT – Camden Recognition
 7 Memory Test; NBV – normalised brain volume; WML – white matter lesion
 8

	Controls	MCI	<i>t</i> statistic (df); <i>p</i>
Age (yrs.)	74.0 (6.5)	76.8 (7.3)	1.3 (43); .19
Education (yrs.)	15 (3)	14 (4)	1.8 (43); .08
NART-R IQ	120 (9)	115 (11)	1.8 (43); .08
Percentage females	50%	44%	
<i>Cognitive measures</i>			
Category fluency	39.5 (10.9)	25.6 (7.9)	4.9 (41); <.001
Verbal fluency	43.2 (13.1)	35.9 (11.3)	1.9 (41); .067
Digit Symbol Substitution	56.5 (18.6)	34.8 (11.9)	4.6 (40); <.001
Stroop suppression	93.4 (19.1)	57.4 (28.2)	4.7 (40); <.001
Tower of London rule violations	1.2 (1.7)	5.8 (4.5)	4.2 (41); <.001
Trails switching	74.0 (31.6)	105.4 (50.7)	2.4 (42); .021
FCSRT free recall	29.3 (8.4)	12.1 (9.7)	6.2 (42); <.001
CRMT face recognition	23.4 (2.8)	20.0 (3.4)	3.6 (41); <.001
<i>MRI – general measures</i>			
NBV (ml)	1,451.4 (57.4)	1,421.7 (57.4)	1.7 (43); .091
WML volume (cm)	15.6 (6.7)	19.6 (10.3)	1.5 (41); .15
<i>Structural network properties</i>			
Global efficiency	0.0260 (0.0021)	0.0239 (0.0036)	2.6 (39.6); .014
Mean clustering coefficient	18.1 (1.9)	16.7 (2.3)	2.2 (43); .037
Small-worldness	1.90 (0.26)	1.95 (.28)	0.63 (43); .53

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Table 2. Univariate relationship between network topology and cognition in patients with MCI and healthy elderly. Pearson product-moment correlations (*r*) of cognitive scores with global efficiency (Eglob) and mean clustering coefficient (C), with parenthetical *p* values. Coefficients shown in bold reach significance after Bonferroni correction for number of network measures (uncorrected $p < .025$), but not number of cognitive tests.

	MCI		Controls	
	Eglob	C	Eglob	C
			<i>r</i> (<i>p</i>)	
Cognitive control				
Category fluency	.56 (.005)	.61 (.002)	.34 (.14)	.20 (.39)
Verbal fluency	.17 (.43)	.33 (.12)	.00 (.99)	-.04 (.87)
Digit Symbol Substitution	.48 (.022)	.40 (.06)	.29 (.23)	.14 (.55)
Stroop suppression	.46 (.025)	.21 (.32)	.26 (.29)	.24 (.33)
Tower of London rule violations	-.04 (.86)	-.12 (.57)	-.04 (.88)	.04 (.88)
Trails switching	-.17 (.44)	-.42 (.041)	-.20 (.40)	-.28 (.24)
Memory				
FCSRT free recall	.28 (.19)	.32 (.13)	.16 (.51)	.00 (.99)
CRMT face recognition	.40 (.05)	.08 (.71)	.16 (.51)	.01 (.96)

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Table 3. Relationship between network topology and cognition in patients with MCI and healthy elderly, adjusting for covariates. Partial correlation coefficients (*r*) of cognitive scores with global efficiency (Eglob) and mean clustering coefficient (C), covarying for age, gender, education, normalised brain volume and total volume of white matter hyperintensities, with parenthetical *p* values. Coefficients shown in bold reach significance after Bonferroni correction for number of network measures (uncorrected $p < .025$), but not number of cognitive tests.

	MCI		Controls	
	Eglob	C	Eglob	C
			<i>r</i> (<i>p</i>)	
Cognitive control				
Category fluency	.41 (.13)	.64 (.011)	.23 (.46)	.28 (.35)
Verbal fluency	.34 (.22)	.42 (.12)	.02 (.96)	.01 (.96)
Digit Symbol Substitution	.73 (.002)	.49 (.06)	.27 (.38)	.15 (.62)
Stroop suppression	.64 (.010)	.26 (.34)	.37 (.21)	.24 (.42)
Tower of London rule violations	-.10 (.74)	-.23 (.41)	.10 (.74)	.05 (.86)
Trails switching	-.04 (.89)	-.53 (.041)	-.22 (.46)	-.33 (.28)
Memory				
FCSRT free recall	.51 (.05)	.47 (.07)	.03 (.93)	.01 (.96)
CRMT face recognition	.29 (.29)	-.02 (.95)	.22 (.46)	-.24 (.42)

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1 **Table 4. Regression models for measures of cognitive control in healthy elderly.**
 2 Models with fractional anisotropy of the left anterior cingulum (1), and additionally a
 3 network measure (2) as predictors. Displayed are standardised regression coefficients (β)
 4 with parenthetical p values.
 5 Eglob – global efficiency; C – mean clustering coefficient.
 6

	Model 1:	Model 2:		β (p)
	Cingulum	Network measure	Cingulum	
Category Fluency	.63 (.003)	<i>Eglob</i> .29 (.11)	.60 (.003)	
		<i>C</i> .23 (.21)	.64 (.002)	
Digit Symbol	.52 (.022)	<i>Eglob</i> .25 (.23)	.50 (.026)	
		<i>C</i> .17 (.43)	.53 (.023)	

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 9 **Table 5. Regression models for measures of cognitive control in MCI.** Models with
 10 mean diffusivity of the left posterior cingulum (1), and additionally a network measure
 11 (2) as predictors. Displayed are standardised regression coefficients (β) with parenthetical
 12 p values.
 13 Eglob – global efficiency; C – mean clustering coefficient.
 14

	Model 1:	Model 2:		β (p)
	Cingulum	Network measure	Cingulum	
Category Fluency	-.66 (.001)	<i>Eglob</i> .32 (.15)	-.47 (.037)	
		<i>C</i> .42 (.020)	-.49 (.008)	
Digit Symbol	-.52 (.016)	<i>Eglob</i> .33 (.17)	-.33 (.18)	
		<i>C</i> .25 (.25)	-.42 (.058)	

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Table 6. Regression models for free recall in healthy elderly and MCI. Models with fornix volume fraction (1), and fornix volume fraction and a network measure (2) as predictors. Displayed are standardised regression coefficients (β) with parenthetical p values.
Eglob – global efficiency; C – mean clustering coefficient

	Model 1:	Model 2:		β (p)
	Fornix	Network measure	Fornix	
Healthy elderly	.63 (.003)	<i>Eglob</i> -.11 (.58)	.68 (.004)	
		<i>C</i> -.29 (.15)	.75 (.001)	
MCI	.39 (.058)	<i>Eglob</i> .09 (.71)	.34 (.17)	
		<i>C</i> .24 (.25)	.33 (.11)	

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Figure 01.TIF

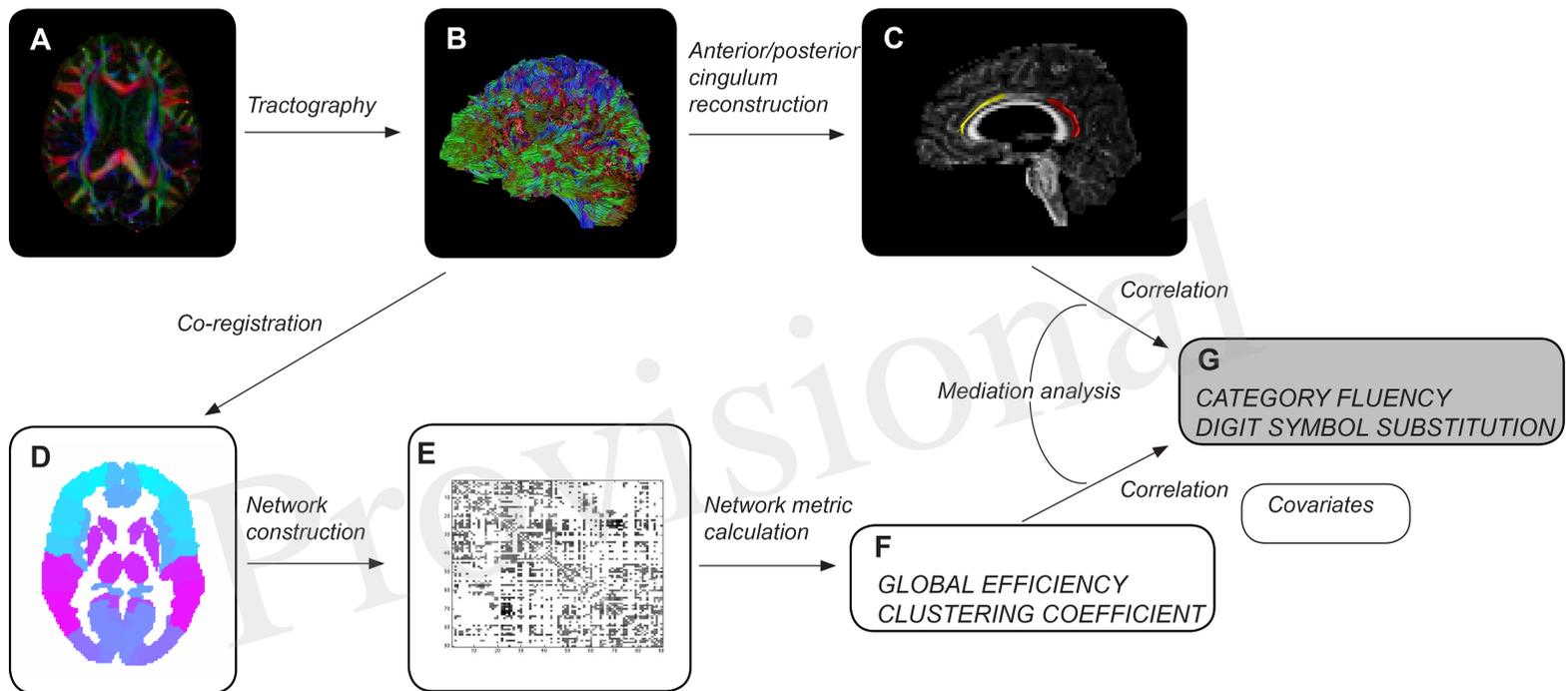
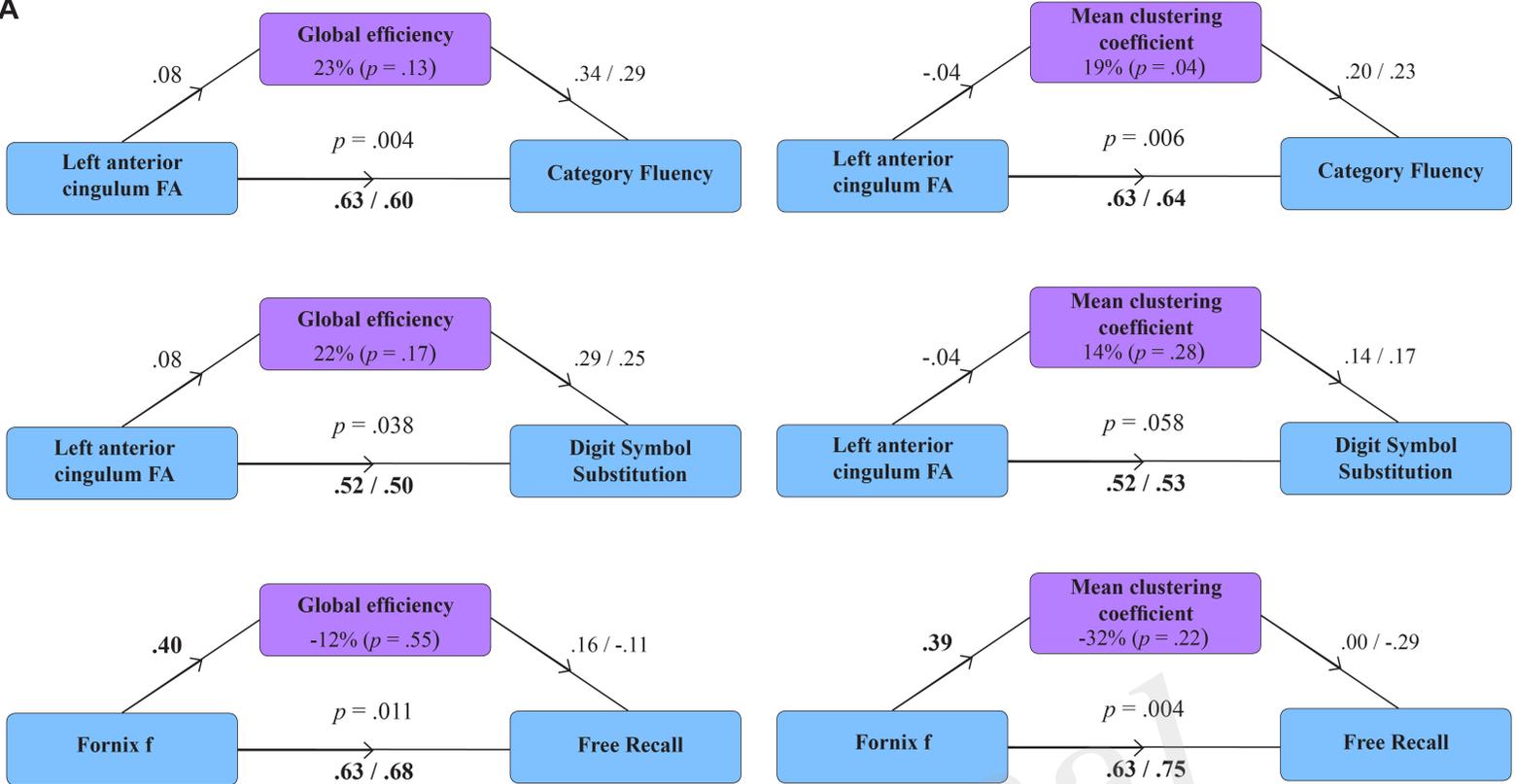


Figure 02.TIF

A



B

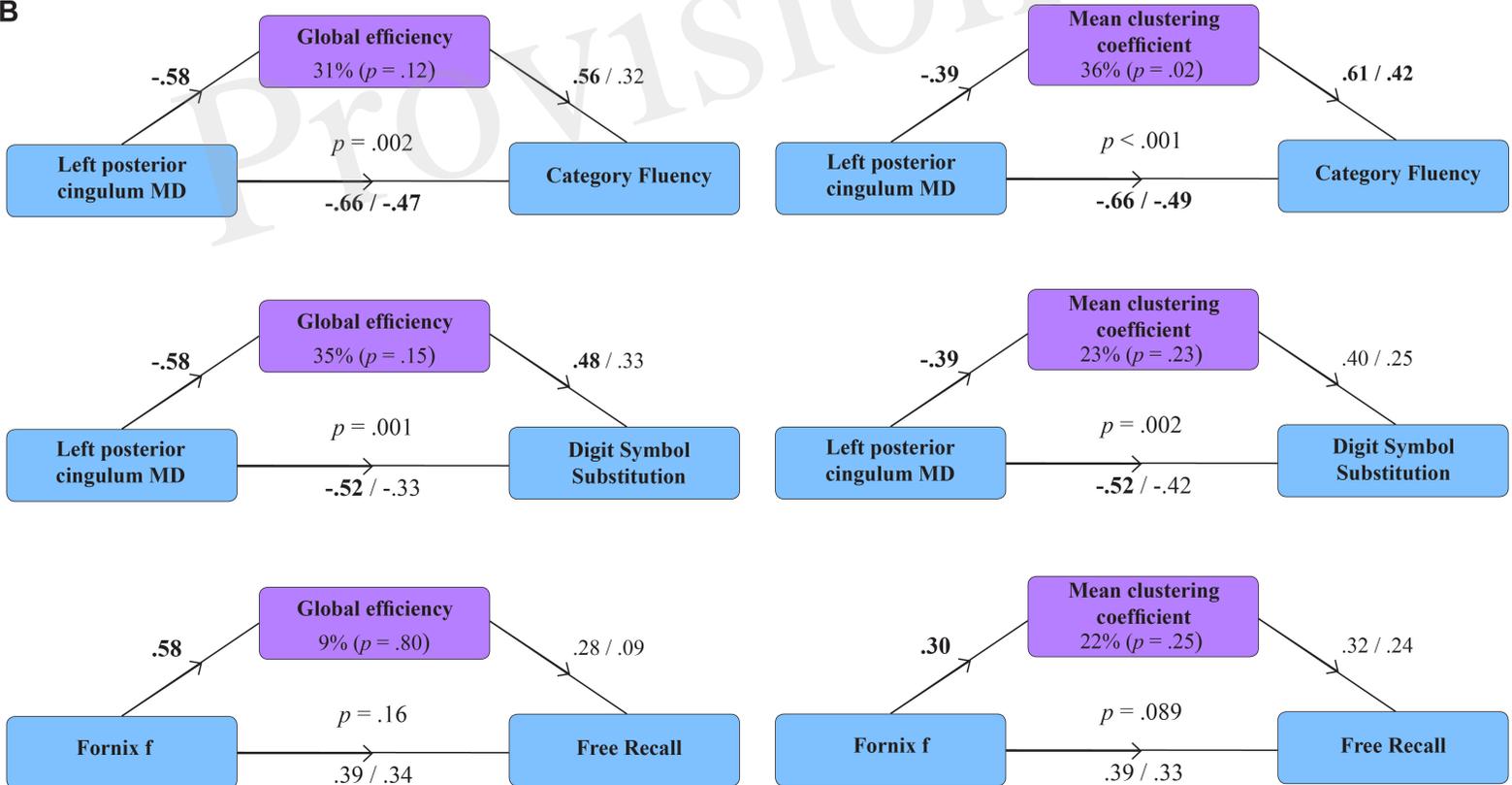


Figure 03.TIF

