Joint impact on attention, alertness and inhibition of lesions at a frontal white matter crossroad

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Abstract

In everyday life, information from different cognitive domains - such as visuospatial attention, alertness, and inhibition - needs to be integrated between different brain regions. Early models suggested that completely segregated brain networks control these three cognitive domains. However, more recent accounts, mainly based on neuroimaging data in healthy participants, indicate that different tasks lead to specific patterns of activation within the same, higher-order and "multiple-demand" network. If so, then a lesion to critical substrates of this common network should determine a concomitant impairment in all three cognitive domains. The aim of the present study was to critically investigate this hypothesis, i.e., to identify focal stroke lesions within the network that can concomitantly impact visuospatial attention, alertness and inhibition.

We studied an unselected sample of 60 first-ever right-hemispheric, subacute stroke patients using a data-driven, bottom-up approach. Patients performed 12 standardized neuropsychological and oculomotor tests, four per cognitive domain. Principal component analyses revealed a strong relationship between all three cognitive domains: 10 of 12 tests loaded on a first, *Common Component*. Analysis of the neuroanatomical lesion correlates using different approaches (i.e., Voxel-Based and Tractwise Lesion-Symptom Mapping, Disconnectome maps) provided convergent evidence on the association between severe impairment of this *Common Component* and lesions at the intersection of Superior Longitudinal Fasciculus II and III, Frontal Aslant Tract and, to a lesser extent, the Putamen and Inferior Fronto-Occipital Fasciculus. Moreover, patients with a lesion involving this region were significantly more impaired in daily living cognition, which provides an ecological validation of our results. A probabilistic functional atlas of the multiple-demand network was performed to confirm the potential relationship between patients'

lesion substrates and observed cognitive impairments as a function of the MD-network connectivity disruption.

These findings show, for the first time, that a lesion to a specific white matter crossroad can determine a concurrent breakdown in all three considered cognitive domains. Our results support the multiple-demand network model, proposing that different cognitive operations depend on specific collaborators and their interaction, within the same underlying neural network. Our findings also extend this hypothesis by showing (1) the contribution of SLF and FAT to the multiple-demand network, and (2) a critical neuroanatomical intersection, crossed by a vast amount of long-range white matter tracts, many of which interconnect cortical areas of the multiple-demand network. The vulnerability of this crossroad to stroke has specific cognitive and clinical consequences; this has the potential to influence future rehabilitative approaches.

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Abbreviations: CoC = Center of Cancellation; FAT = Frontal Aslant tract; FDR = false discovery rate; FVE = Free visual exploration; HfG = Humanforschungsgesetz; HRA = Swiss Human Research Act; IFOF = Inferior Fronto-Occipital Fasciculus; LIMOS = Lucerne ICF-Based Multidisciplinary Observation Scale; MD = multiple-demand; PCA = Principal Component Analysis; SLF = Superior Longitudinal Fasciculus; TAP = Testbatterie für die Aufmerksamkeitsprüfung; TLSM = Tractwise Lesion-Symptom Mapping; VLSM = Voxel-Based Lesion-Symptom Mapping

Introduction

A dynamic interaction between different cognitive functions is the basis of everyday behaviour. Cognitive functions are recruited depending on the situation's requests and alternate in action upon environmental changes. Hereby, information from various cognitive domains needed for this complex behaviour, such as alertness (e.g. the preparedness to respond to stimuli from the environment[151]), visuospatial attention (e.g. the voluntary or automatic orientation of attention towards visual targets across space[54]) and inhibition (e.g. the ability to withhold a response that is not suitable given the changing environmental information[161] needs to be shared and integrated between different brain areas.

Initial concepts have suggested that the cognitive domains of visuospatial attention, alertness and inhibition are controlled by distributed, separate neural networks. For instance, a ventral and dorsal visual attention network,[1] a vigilant attention network[2] and an inhibitory control network[3] have been described.

In other accounts, the functional connections between visuospatial attention, alertness and inhibition have led to the assumption that these cognitive domains depend on at least partially shared neural networks, as described in the fronto-parietal control network,[4] the superordinate cognitive control network[5] or, more recently, in the higher-order, "multiple-demand" (MD) network (e.g.[6-9]). These network models encompass similar cortical regions, such as the lateral frontal surface, the dorsomedial frontal cortex (including presupplementary motor area and dorsal anterior cingulate), areas in and around the anterior insula, the intraparietal sulcus, and often also a region at the occipitotemporal border.[4-6]

The close functional and anatomical relationship between visuospatial attention, alertness and inhibition has mainly been described in healthy subjects.[6-8,10] This leads to the hypothesis that these cognitive functions should often be concomitantly impaired in patients with brain lesions, for example after stroke. This hypothesis is in line with results from observational studies in patients with right-hemispheric lesions and signs of spatial neglect, in whom visuospatial attention towards the contralesional space is typically impaired, and a concomitant decrease in alertness and inhibition seems to be often associated (e.g.[11-14]).

In the present study, we aimed to investigate whether and how strongly the three considered cognitive domains (i.e., visuospatial attention, alertness, and inhibition) relate to each other, behaviourally and at the neuroanatomical level, in stroke patients. More precisely, we aimed to investigate whether impairments in these three cognitive domains co-occur in stroke patients and whether this co-occurrence can be explained by a lesion to a common neural substrate.

These three cognitive domains were chosen based on their importance for successfully performing activities of daily living.[15,16] Previous studies have separately shown that these three cognitive domains are often impaired after right-hemispheric brain lesions (e.g.[2,17-19]). Hence, we applied a data-driven, bottom-up approach in a sample of 60 first-ever, right-hemispheric, subacute stroke patients. For each patient, four standardized and commonly used neuropsychological and oculomotor tests were administered to comprehensively assess each of the three cognitive domains: visuospatial attention, alertness, and inhibition (resulting in a total of twelve tests). A principal component analysis (PCA) assessed the patients' common patterns of performance across the twelve tests. Three lesion analysis techniques (Voxel-Based Lesion-Symptom Mapping (VLSM), Tractwise Lesion-Symptom Mapping (TLSM), and Disconnectome

maps) determined the lesion and network correlates of the performance components. Finally, cognition during daily living[20] was assessed by independent therapists, who were blind with respect to the study aims, in order to compare and ecologically validate the measures obtained on a test level with measures of cognitive performance in everyday life. Conclusively, an analysis using a probabilistic functional atlas of the multiple-demand network[149,150] was performed to confirm the potential relationship between the patients' lesion substrates and the observed cognitive impairments as a function of the MD-network connectivity disruption.

Materials and methods

Patients

Sixty patients with a first-ever subacute right-hemispheric stroke were included in this prospective study (25 female; mean age=74.400 (SD=10.081, range 50-90); days since stroke mean=19.783 (SD=10.441, range 5-65); years of education mean=11.183 (SD=2.633, range 6-16); 91.667 % right handed (2 left handed, 1 ambidexter, 2 originally left-handed but retrained to right); 43 ischemic, 17 haemorrhagic stroke), an overlay plot of the lesions of all 60 patients is shown in Supplementary Figure 1. All patients were admitted to the Neurocenter of the Cantonal Hospital in Luzern, Switzerland, to receive multidisciplinary inpatient neurorehabilitation, and were consecutively enrolled in the study after giving informed consent between January 2018 and March 2020.

Apart from a history of first-ever right-hemispheric stroke, the main inclusion criteria were age above 18 years, normal or corrected-to-normal visual acuity and being able to undergo an MRI scan. Exclusion criteria were the presence of other neurological diseases (e.g., epilepsy, multiple sclerosis, tumour, etc.), major psychiatric disorders and alcohol/drug abuse (Figure 1). By excluding left-hemispheric stroke patients, who often show aphasia and/or other language disorders[21], we aimed to ensure not to confound our results with difficulties in understanding the task instructions.

The study followed the STROBE guidelines for reporting observational studies[22] and was conducted in accordance with the principles laid down in the Declaration of Helsinki (WHO,

2013). The study was approved by the local Ethics Committee (Ethics Committee Nordwest and Zentralschweiz, Switzerland).

Behavioural Data Acquisition and Analysis

For each patient, four standardized and commonly used neuropsychological and oculomotor tests were administered to comprehensively assess each of the three cognitive domains visuospatial attention, alertness, and inhibition (resulting in a total of twelve tests, summarized in Table I). To assess visuospatial attention, the Letter Cancellation Test (center of cancellation (CoC) of cancelled items),[23] the Line Bisection Test (mean relative deviation from actual midline),[24] the Five-Point Test (CoC of drawn designs),[25] and video-oculography during free visual exploration (FVE; mean gaze position[26,27]) were performed. Alertness was assessed by means of two subtest of a computerized, validated attention test battery (median reaction time in tonic and phasic Alertness of the Testbatterie für die Aufmerksamkeitsprüfung, TAP[28]) and two outcome variables of the FVE paradigm (mean fixation duration,[29] and peak saccade velocity[30]). To investigate inhibition, three neuropsychological measures (perseverative errors in the Five-Point Test[25], number of errors in a Go-Nogo task,[31,32] number of errors in the Stroop interference task[33,34]) and one video-oculographic measure (false responses in the antisaccade task[35,36]) were used.

For a detailed description of the 12 neuropsychological tests and the respective outcome variables, as well as of the video-oculography paradigms and apparatus, please see the Supplementary Material.

Statistics

To allow a direct comparison between variables, all outcome variables were z-transformed, based on the normative values of the respective healthy control groups.[13,28,31,34,35,37-40]

Descriptive Statistics

The results of all outcome variables were plotted by means of violin wrapping box-and-whisker plots, to qualitatively evaluate the overall variability of the outcome variables included.

Furthermore, for each patient, the severity of deficits within each cognitive domain was plotted by means of the number of clinical significant test results (i.e., how many out of the 4 tests per cognitive domain (i.e., 12 in total) had standardized scores of z<-1.5, as defined with respect to the performance of healthy controls[152]; see Table 1 for references to the respective normative data sets) using box-and-whisker plots.

Principal Component Analysis

A PCA was performed in order to explore potential common factors underlying the three cognitive domains (visuospatial attention, alertness, and inhibition) investigated in our data sample.

As a part of the PCA, Pearson's correlations coefficients were computed and tested for significance (1-tailed) between all pairs of outcome variables. Then, the PCA was conducted on the 12 outcome variables (as described in Table I) without rotation. The Kaiser–Meyer–Olkin measure was used to verify the sampling adequacy for the analysis.[41] The Bartlett's test of sphericity was used to investigate whether the correlations between the 12 outcome variables were sufficiently large for a PCA. Kaiser's criterion was used to define the number of components that were retained in the final analysis.

In the PCA, missing data were replaced by the function 'mean', as implemented in SPSS 27 (number of missing data replaced: FVE n=3; Five-Point Test n=2; antisaccade task n=6; TAP tonic/phasic Alertness n=2; Go-Nogo n=3; STROOP n=6). All outcome variables with a factor loading of ≥.40 on a given component were considered as relevant.[41,42] The patients' individual factor values per component were then computed and used as predictors for the voxel-based lesion-symptom mapping (VLSM) analysis, as described in the following.

For all analyses, a p-value of <0.05 was considered as statistically significant.

Neuroanatomical Data and Analysis

MRI acquisition and Lesion mapping

High-resolution MRI were acquired in all patients, using two sequences: 1) a fluid-attenuated inversion-recovery (FLAIR) sequence (TR/TE=5000/389 msec, slice thickness=0.9mm, voxel size=0.4x0.4x0.9 mm), which was used for identification and demarcation of lesions; 2) a

magnetisation prepared rapid acquisition gradient echo (MPRAGE) sequence (TR/TE=2240/3.72 msec, slice thickness=0.9 mm, voxel size=0.9x0.9x0.9 mm), which was used to enhance the quality of normalisation. Lesion mapping was performed as outlined in Karnath et al. 2011.[43] In short, lesions were manually delineated on the patients' individual MRI images using the MRIcron software (http://www.mccauslandcenter.sc.edu/crnl/tools). Images were then normalised into the Montreal Neurological Institute (MNI) space using the Clinical Toolbox for SPM12 ([44]; https://www.nitrc.org/projects/clinicaltbx/), applying enantiomorphic normalization ([45]; SPM12 http://www.fil.ion.ucl.ac.uk/ spm; MATLAB, MatWorks Inc., Natick, MA, United States).

We used Voxel-Based Lesion-Symptom Mapping (VLSM) to establish causal inferences between behaviour and underlying neuroanatomical structures.[46-48] Combined lesion analysis and (dis)connectome analysis, using TLSM and Disconnectome maps, were further used to determine whether lesions at different sites causing similar symptoms were located within the same neural network.[46,49]

Voxel-Based Lesion-Symptom Mapping (VLSM)

Previous studies showed that 3D MRI scans are highly valuable in assessing the relationship between disconnected areas and the patients' neuropsychological performance.[49] To establish the potential brain-function relationship between lesion location and PCA results, standard voxel-based lesion-symptom (VLSM) analyses were conducted using the open source NPM software (http://www.cabiatl.com/mricro/npm/). VLSM was conducted using the Bruner-Munzel test for continuous behavioural data,[50] using the individual factor values for each component as derived from the PCA, as described above (Principal Component Analysis). Only voxels that were lesioned in ≥20% of the patients were included in the analysis, and multiple comparisons were controlled for using a permutation-based threshold, applying 4000 iterations.[51,52] The significance threshold was adjusted by means of a false discovery rate (FDR) approach (criterion of 0.05) in order to control for type I error.

Tractwise Lesion-Symptom Mapping (TLSM)

The significant lesion clusters predicting PCA factor values, as identified by the VLSM analyses, were located within the cerebral white matter (see results in Voxel-Based Lesion-Symptom

Mapping (VLSM)). Therefore, Tractotron (a part of the BCBtoolkit[49], http://www.toolkit.bcblab.com/) was used to compute the probability that specific tracts would be affected by the lesions, as well as to calculate the damaged proportion of the respective tracts for each patient. Among the 68 white matter tracts available in the BCBtoolkit library, we selected the tracts that showed an overlap with the significant lesion clusters predicting PCA factor values in the VLSM analyses. These tracts were: the Frontal Aslant tract (FAT), the Superior Longitudinal Fasciculus II (SLF II), the Superior Longitudinal Fasciculus III (SLF III) and to a lesser extent the Inferior Fronto-Occipital Fasciculus (IFOF).

Based on the VLSM results, we assumed that white matter tract disconnections would result in a decline of cognitive performance, as reflected by the factor values in the respective PCA component. Therefore, one-tailed Pearson's correlations (Bonferroni-corrected for multiple comparisons) were calculated between PCA factor values and disconnection probabilities, as well as the damaged tract proportions, for each white matter tract.

Disconnectome maps

In order to account for potential effects beyond focal lesions, Disconnectome maps were calculated using the BCBtoolkit.[49] The toolkit includes healthy control subjects' diffusion weighted imaging datasets,[53] which are used to estimate the fibres passing through each lesion. For each of the 60 patients included in the present study, tractography was estimated as described by Thiebaut de Schotten and colleagues.[54] In brief, each patient's lesion was registered to native space of the healthy control group, using affine and diffeomorphic deformations,[55,56] and subsequently used as seed for the tractography in Trackvis (http://trackvis.org/). Tractographies from the lesions were then transformed in visitation maps,[54] binarised, and brought to MNI space. The corresponding percentage overlap map was computed by summing the normalized visitation map of each healthy control subject at each point in MNI space. Hence, in the resulting Disconnectome map of each individual patient, the value in each voxel considers the interindividual variability of tract reconstructions in the healthy control group. The value for each voxel indicates the probability of disconnection, ranging from 0 to 100%, for a lesion in each individual patient.[57]

To establish the potential relationships between white matter tract disconnections (as reflected by Disconnectome maps) and behavioural correlates (as reflected by PCA results), a standard

VLSM analysis for continuous data was conducted on the Disconnectome maps, with the same procedures described above (*Voxel-Based Lesion-Symptom Mapping (VLSM*)). For this purpose, we used a region of interest (ROI) approach. The ROI was defined as the total, summed extension of the tracts that intersected a significant lesion cluster predicting PCA factor values, as identified in the first series of VLSM analyses.[53,54] These tracts were the FAT, SLF II, SLF III and IFOF. To define the ROI, the probability for voxels to belong to a given tract was set at >50%).

Test-Level Cognition and Cognition During Daily Living

First, in order to establish the potential relationship between PCA results and cognitive performance, PCA loadings were correlated with the number of tests showing clinical relevant impairment ($z < -1.5$) in the three considered cognitive domains (visuospatial attention, alertness, and inhibition).

Second, in order to investigate the relationship between cognitive performance as reflected by test results and as observed in daily living, the Lucerne ICF-Based Multidisciplinary Observation Scale (LIMOS) was used.[20,58] The LIMOS is a sensitive, reliable and valid scale for the multidisciplinary observation of stroke patients' ability to perform activities of daily living[20], which includes four subscales: motor, cognition, communication, and domestic life. Thereby, the LIMOS cognition subscale consists of 15 items observing cognitive functions in daily living, such as planning tasks, solving simple problems, and making decisions.[20] Each item is scored from 1 (“patient is not able to fulfil a task or needs assistance up to 75%”) to 5 (“patient is able to fulfil tasks independently”), leading to a score ranging from 15 to 75.[20] The LIMOS was rated by independent therapists, who were blind with respect to the study aims. In order to investigate the potential relationship between PCA factor values and cognition during daily living (as reflected by the LIMOS cognition subscale), Pearson’s correlations were calculated (2-tailed). Additionally, to investigate whether cognition during daily living is influenced by the volume of the affected brain area, a partial correlation was calculated between test-level cognition (as represented by PCA values) and LIMOS cognition subscale scores, while controlling for lesion volume (2-tailed).

Third, to confirm the potential relationship between lesions to critical cerebral substrates and cognitive performance in daily living, we compared the LIMOS cognition subscale scores

between patients with versus without a lesion including the significant lesion clusters predicting PCA factor values (i.e., SLFII, SLF III, FAT intersection and Putamen/IFOF, as identified in the *Voxel-Based Lesion-Symptom Mapping Analysis*). The scores were statistically compared by means of an independent-samples t-test.

Functional Connectivity

To confirm the potential relationship between the patients' lesion substrates and the observed cognitive impairments (test-level cognition and cognition during daily living) as a function of the MD-network connectivity disruption, we used a probabilistic functional atlas of the multiple-demand network[150] and calculated MD-weighted lesion volumes.[149] In short, the probabilistic functional atlas contains the probability to belong to the multiple-demand network for any given location in the brain. Hauptman et al.[150] constructed the probabilistic functional atlas using data from 691 healthy participants. The atlas includes voxels with a network probability range of 0.001 to 0.75, representing the "proportion of participants for whom that voxel belongs to the top 10% of localizer-responsive voxels". Each of our patient's lesion was weighted with respect to the probabilistic functional atlas,[149,150] and the corresponding MD-weighted lesion volume was correlated with test-level cognition (represented by PCA factor values) as well as with cognition during daily living (as reflected by the LIMOS cognition subscale scores; 2-tailed, non-parametric correlation was applied after visual inspection of the distribution of the MD-weighted lesion volume).

Data availability

The conditions of our ethics approval do not permit the public archiving of the data supporting the conclusions of this study. Based on the Swiss Human Research Act, HRA (Humanforschungsgesetz, HfG) in Switzerland, readers seeking access to the data and the study materials must therefore complete a formal data sharing agreement to obtain the data. Interested readers should contact the corresponding author for more information and help.

Results

Descriptive Statistics

The violin wrapping box-and-whisker plots, depicting the patients' individual severity of deficits in all considered cognitive domains and variables, revealed a broad variability across patients (Figure 2). Heterogeneous distributions were found in all three cognitive domains: visuospatial attention, alertness, and inhibition. A similar pattern was observable in the box-and-whisker plots (*Supplementary Figure 2)*, depicting the number of tests in which individual patients showed a clinical relevant impairment (i.e., z<-1.5).

Principal Component Analysis (PCA)

First, in order to investigate whether patients with higher impairment in one cognitive domain also presented with increased deficits in other cognitive domains, Pearson's correlations were computed. Pearson's correlations between all pairs of outcome variables showed significant results for several variable combinations (Figure 2B). Hereby, outcome variables of the visuospatial attention domain correlated with each other, but also with some of the outcome variables associated with the alertness and the inhibition domain.

These results suggest, at least for some of the considered variables, the existence of common underpinnings for all three cognitive domains. Hence, in order to explore in a more systematic way the common underlying components of the considered cognitive domains, a PCA was computed.

For the PCA including all 12 outcome variables, the Kaiser–Meyer–Olkin measure (KMO=.720; to be interpreted as "good"[41]) supported the sampling adequacy for the analysis. Bartlett's test of sphericity ($\chi^2(66)=187.863$, $p < .001$) indicated that the correlations between outcome variables were sufficiently large for the PCA to be performed. An initial analysis was run to obtain eigenvalues for each component in the data. Three components had eigenvalues above Kaiser's criterion of 1, and in combination explained 56.341% of the total variance (component 1 explaining 34.175%, component 2 explaining 12.093%, and component 3 explaining 10.073% of the variance, respectively; Figure 2C).

Ten out of the 12 variables showed medium to strong loadings on the first component (all factor loadings ≥.431; Figure 2C). Four out of these ten variables belonged to the visuospatial attention domain (Letter CoC,[38] mean gaze position during FVE,[27] Line Bisection,[59] CoC in the Five-Point Test[13]), three to the alertness domain (phasic Alertness,[28] tonic Alertness,[28] Fixation Duration[60]), and three to the inhibition domain (Perseverations in the Five-Point Test,[13] Go-Nogo,[32] and Antisaccade Errors[35]). Therefore, this component was named *Common Component*.

The outcome variables that clustered on the second component (all factor loadings ≥.722) belonged to the alertness (FVE peak saccade velocity[30]) and the inhibition (Stroop[33,34]) domains, and were therefore named *Inhibition/Alertness Component*. A third component consisted of all four variables belonging to the alertness domain, namely phasic Alertness, tonic Alertness, Fixation Duration and FVE peak saccade velocity (all factor loadings ≥.408), and was therefore named *Alertness Component*.

Neuroanatomical Data

Voxel-Based Lesion-Symptom Mapping (VLSM)

To ascertain whether the three PCA components would rely onto discrete anatomical substrates, VLSM analyses were performed. For the *Common Component* (i.e., the first PCA component), the analysis revealed a total of 325 significant voxels (0.33cm^3 in total). A larger cluster was located in the FAT, the SLF II, and the SLF III (MNI coordinates of the centre of mass of the cluster: 28, -2, 26, located at the intersection of the right SLF II (probability of the significant voxels to belong to SLF II of 90%[54]), the right SLF III (probability of 100%[54]) and the right FAT (probability of 100%;[54] Figure 3A, top row)). It is of note, that a comparison of the location of the critical lesion cluster lying within the SLFII/III/FAT intersection and the location of the maximum lesion overlap (see Supplementary Figure 3) shows that these two locations do not match. This speaks against a simple bias in terms of a non-specifically higher frequency of lesions in the area of the identified critical cluster.

A smaller cluster found in the Putamen and the IFOF (MNI coordinates of the centre of mass of the cluster: 30, 16, 2, involving the right SLF III (probability of 100%[54]), the right Inferior

Fronto-Occipital Fasciculus (IFOF; probability of 96%[54]) and the putamen (probability of 84%, according to the MNI structural Atlas[61,62]; Figure 3A, bottom row).

VLSM analyses for the second and the third PCA component, i.e., the *Inhibition/Alertness Component* and the *Alertness Component*, did not yield any significant results.

Because only the *Common Component* showed significant lesion correlates, further neuroanatomical lesion analyses were performed only on this component.

Tractwise Lesion-Symptom Mapping (TLSM)

For the *Common Component*, the Bonferroni-corrected Pearson's correlations (i.e., corrected considering 4 comparisons, corresponding to the main intersection found in the VLSM analysis, including the three tracts SLF II, SLF III, and FAT, as well as the IFOF from the second, smaller VLSM cluster; resulting in a corrected critical p-value of ≤0.0125) revealed that impaired cognitive performance (represented by lower factor values) significantly correlated with a higher disconnection probability, as well as with an increased damaged tract proportion, within all the four-considered white matter tracts (Disconnection probability: FAT r=-0.322, p=0.012; SLF II r=-0.299, p=0.020; SLF III r=-0.373, p=0.003; IFOF r=-0.378, p= 0.003. Damage proportion: FAT r=-0.442, p<0.001; SLF II r=-0.369, p=0.004; SLF III r=-0.390, p=0.002; IFOF r=-0.397, p=0.002).

Disconnectome maps

The ROI-restricted Brunner-Munzel test including the PCA factor values of the *Common Component* revealed that patients presenting with more severe cognitive impairment (represented by lower factor values) were more likely to show a lesion at the intersection of SLF II, SLF III, and FAT white matter tracts, as well as along the FAT, the SLF III and the IFOF (significant lesion cluster with a total volume of 1640 voxels, 1.64cm^3;[54] Figure 3B). The largest cluster was found to belong to the FAT (702 voxels, 1.455% of the FAT tract), followed by SLF III (937 voxels, 0.982% of the tract), IFOF (328 voxels, 0.436% of the tract) and SLF II (164 voxels, 0.175% of the tract).

Test-Level Cognition and Cognition During Daily Living

The factor values of the *Common Component* were significantly correlated with the number of tests showing clinical relevant impairment (i.e., z <-1.5) in the three cognitive domains, respectively: visuospatial attention (r=-.783, p<.001), alertness (r=-.687, p<.001), and inhibition (r=-.661, p<.001). To illustrate these results, we plotted the number of tests showing a clinical relevant impairment in each considered cognitive domain against the factor values of the *Common Component* (Figure 4, top). These plots showed that patients with smaller PCA values (y-axis) also showed a higher number of clinical relevant deficits in all three cognitive domains (as represented by darker colour shades; visuospatial attention (blue), alertness (yellow) and inhibition in (grey)).

In a next step, we aimed to ecologically validate the results, ascertaining whether they would extend beyond the clinical assessments level, i.e., whether patients with more severe deficits on a test level (represented by the factor values of the *Common Component*) and a brain lesion involving the intersection of the SLF/FAT and the Putamen/IFOF (as suggested by the VLSM analysis) would also show more severe cognitive deficits in the activities of daily living. Hence, to further move towards such real-world scenarios, cognition during daily living was assessed by independent therapists, and a potential transfer effect from the level of clinical test scores (i.e. the *Common Component*) to the level of cognition in everyday behaviour (i.e. LIMOS cognition) was investigated using Pearson's correlation. Our results showed that patients with more severely impaired test-level cognition (as represented by lower PCA values) also presented with more severely impaired cognition during daily living (r=.575, p<.001; Figure 4, bottom; a partial correlation controlling for lesion volume revealed the same significant result, r=.548, p<.001, showing that lesion volume was not a major determinant for this relationship).

Finally, we compared LIMOS cognition scores between patients with versus without lesion in the SLFII/SLFIII/FAT and Putamen/IFOF Cluster (as indicated by the neuroanatomical analysis presented above), and found that LIMOS cognition was significantly more severely impaired in patients whose lesion lied within the SLFII/SLFIII/FAT and the Putamen/IFOF Cluster (t(58)=-2.101, p=.040; n=31 with a lesion within the cluster, represented by red triangles in Figure 4,

bottom, mean=32.23, SD=11.40; n=29 without a lesion within the cluster, represented by black circles in Figure 4, bottom panel, mean=38.93, SD=13.30).

Functional Connectivity

To confirm the potential relationship between the critical cerebral substrates of the MD-network we used a probabilistic functional atlas[150] to calculate the MD-weighted lesion volume.[149] The corresponding MD-weighted lesion volume significantly correlated with test-level cognition (represented PCA factor values; Spearman-Rho =-.295 , p=.022) as well as cognition during daily living (as reflected by the LIMOS cognition subscale; Spearman-Rho =-.312 , p=.015). This supports our previous neuroanatomical and behavioural results suggesting that a lesion involving the MD network is associated with impaired cognition on a test-level as well as during daily living.

Discussion

The aim of the present data-driven study was to investigate how the three cognitive domains of visuospatial attention, alertness and inhibition relate to each other, both on a behavioural and neuroanatomical level. To this end, each cognitive domain was comprehensively assessed by means of four standardized and commonly used neuropsychological and oculomotor tests, within a large, heterogeneous sample of first-ever right-hemispheric subacute stroke patients. The PCA demonstrated that the three cognitive domains are strongly related to each other: ten out of the 12 tests loaded on a first, *Common Component*. Besides, two tests loaded on a second, *Inhibition/Alertness Component*, and four tests loaded on a third, *Alertness Component*.

Next, we assessed the neuroanatomy of the lesions underlying these three components. VLSM analyses using factor loadings of the *Inhibition/Alertness Component* or the *Alertness Component* did not reveal any significant effects. However, the VLSM analysis using the factor loadings of the *Common Component* revealed that right-hemispheric stroke patients presenting with more severe cognitive impairment were significantly more likely to show a lesion involving the intersection of the SLF II, SLF III, and FAT (larger cluster), as well as the right SLF III and some voxels in the anterior part of the putamen and the IFOF (smaller cluster).

In line with these results, further analyses with TLSM and Disconnectome maps revealed that impaired cognitive performance in the *Common Component* significantly correlated with a higher disconnection probability, as well as an increased damaged tract proportion, within the SLFII, SLFIII, FAT, and Putamen/IFOF.

To ecologically validate these findings, we next asked how a lesion involving the intersection of SLFII/SLFIII/FAT and the Putamen/IFOF would influence cognition during daily living. To this end, independent clinicians, who were blind to the study aims, evaluated the cognitive part of the LIMOS.[20,58] Our results revealed that patients with more severely impaired test-level cognition (represented by the factor values of the *Common Component*) and a brain lesion involving the intersection of the SLFII/SLFIII/FAT and Putamen/IFOF also presented with significantly more severely impaired cognition during daily living.

A further analysis using a probabilistic functional atlas of the multiple-demand network[149,150] indicated a relationship between the patients' lesion substrates and the observed cognitive impairments as a function of the MD-network connectivity disruption.

Cognitive Tests

On a behavioural level, the present study revealed a heterogeneous distribution of cognitive test results in our unselected patient sample. This pattern is typical for studies investigating cognition after stroke, reflecting the heterogeneity of deficits and their severity on an individual level, which are partially associated with specific lesion locations, as shown in previous studies.[63]

Crucially, however, our analyses were able to identify within this heterogeneity a common ground between cognitive impairments in visuospatial attention, inhibition, and alertness. Indeed, correlational analyses revealed significant results not only between outcome variables within the same cognitive domain, but also between outcome variables belonging to different cognitive domains. Moreover, our PCA revealed a meaningful and coherent behavioural component (the *Common Component)* that entailed outcome variables of all three cognitive domains and on which 10 out of the 12 outcome variables loaded.

All four visuospatial attention outcome variables and three out of four alertness outcome variables loaded on the *Common Component*. Our bottom-up analyses in a large and unselected patient group thus supports the view of a strong interplay between visuospatial attention and

alertness, proposed by previous studies both in healthy subjects and in stroke patients.[64-67] As a novel and important finding, in addition three typical inhibition outcome variables (false responses in the antisaccade task, errors in the Go-Nogo task, perseverative errors in the Five-Point Test) also loaded on the same PCA component. These three tests involve reactive inhibition to a stimulus, and a component of proactive inhibition when anticipating the possibility of cancelling a prepared action.[68] More precisely, the patient must intentionally supress an action, such as looking at an appearing target in the antisaccade task, imitating a hand movement in the go-no go test, or repeating a design in the five-point test. It is therefore plausible to postulate that this kind of inhibition, which is intentional, controlled, and effortful, is supported by visuospatial attention and alertness. Furthermore, focused visuospatial attention, combined with high alertness and resistance to distraction, are important aspects common to many cognitive tasks.[8,69-71]

Although proactive, goal-directed inhibition is also an important component of the Stroop task,[68] additional functions, such as response selection under competition, are necessary to accomplish this task. Moreover, in order to suppress a prepotent response (reading the word) and name the colour of the ink in which the word is written instead, conflict resolving is mandatory.[72] These might be possible reasons as to why the Stroop task did not load together with all the other outcome variables, but instead, together with the alertness measure of peak saccade velocity, loaded on a second, independent component (i.e. *Inhibition/Alertness Component)*. Hereby, fatigue, reflected in a decrease in saccade velocity,[40,73,74] may result in more frequent inhibition failures, which is also a well-known phenomenon.[75] Also, peak saccade velocity has been discussed in the context of cognitive control. For example, in case of an already initiated saccade, a lower peak velocity may reflect an effort to inhibit the error as it is being executed.[76] In line with this suggestion, the present results revealed that patients who were not able to inhibit cognitive interference (as reflected in an increase in errors in the Stroop task) also showed a reduced ability to sustain saccadic performance (as represented in an increase in peak velocity).

Finally, all four alertness tests loaded on a third *Alertness Component*, which demonstrates the strong link between different aspects of alertness.[28-30] Indeed, the TAP phasic and tonic alertness test is widely used in adult clinical neuropsychology, and previous studies showed a close connection between the two measures.[66] Also, mean visual fixation duration[77] and peak saccade velocity[78] are known to be a sensitive index of the degree of alertness.

Brain networks

To investigate the neuroanatomical landmarks related to the PCA *Common Component*, three conclusive analyses were performed: VLSM, TLSM, and Disconnectome map analyses. All three analysis approaches consistently showed that patients presenting with more severe cognitive impairments in the *Common Component* were also significantly more likely to show a lesion involving the intersection of the SLF II, SLF III, and FAT, as well as the Putamen/IFOF. The VLSM analysis further revealed that the majority of the significant voxels was associated with the FAT, the SLF II and the SLF III.

The SLF II, SLF III, and FAT interconnect the inferior parietal lobule (IPL), the superior temporal gyrus (STG), the frontal eye field (FEF), the inferior frontal gyrus (IFG) and the pre-supplementary motor area (pre-SMA[1,54,64,79-86]). This extended network of interconnected cortical areas is thus compatible with the idea of their relevance not only to a single, but rather to several cognitive domains. Indeed, the IPL, STG, FEF, IFG, and pre-SMA are all nodes of the cortical network subserving visuospatial attention (e.g., [1,87-96]). Furthermore, alertness has been shown to be regulated by the identical cortical areas (IPL;[19,97] STG;[98,99] FEF;[100,101] IFG;[66,102] pre-SMA;[103]). Finally, the IPL,[104,105] STG,[106-108] FEF,[109,110] IFG,[17,111-113] and pre-SMA[81,114-116] have also been associated with inhibition control.

Supplementary analyses (Supplementary Figure 4 a-f and Supplementary Table 1) confirmed this notion: separate VLSM analyses, one for each outcome variable, led to significant clusters in different areas, but crucially also to a common FAT/SLFII/SLFIII intersection over all three cognitive domains.

Some of the parietal and frontal areas are also anatomically connected to the putamen. For instance, a study using fibre tractography[117] has evidenced connectivity between the putamen and the IFG, as well as with rostral parietal areas, such as SMG at the border of STG.[117] The putamen has been shown to be involved in visuospatial attention,[90,117-119] and has also been suggested as a central component of the frontal-subcortical circuit involved in inhibitory processes of executive control.[68,120] In this context, previous studies described the putamen as a hub connecting the networks subtending the control of visual attention and inhibition.[13,117,121] Finally, the putamen has also been reported to be involved in alertness.[122,123]

The IFOF, which has been attributed to the ventral pathway of the human brain,[160] mainly connects the frontal (IFG, MFG, dlPFC[153]) with the occipital lobe.[53] However, the anatomic dissection of the IFOF[154] and probabilistic tract-to-region connectome matrices[162] further identified terminations in the IPL, and the posterior part of the temporo-basal area. The IFOF has also been shown to contribute to visuospatial attention,[155-157] as well as inhibition[159] and alertness.[158]

Taken together, our findings show that visuospatial attention, alertness, and inhibition are tightly connected not only on a behavioural, but also on a neuroanatomical level. A lesion to a discrete white matter location, coinciding with the crossroad of specific white matter tracts, seems to be able to determine a concurrent functional breakdown in all three domains. We therefore argue that beyond the historical segregated networks for alertness, visuospatial attention and inhibition, a common component/network is involved in these cognitive domains. This novel and intriguing finding is strongly reminiscent of the "multiple-demand" (MD) network model. Indeed, cognitive operations have been suggested to depend on different collaborators and their interaction, combining an underlying MD activity with more specialized systems.[8,124,125] Also, on a neuroanatomical level, studies in humans (e.g.[126]) and primates (e.g.[127,128]) revealed common activation patterns in MD regions encoding information across very different tasks.[6] Furthermore, cortical areas commonly reported as belonging to the MD network, reflecting the co-recruitment by multiple task demands in fMRI studies[6,8] are identical to the cortical regions connected by the SLF II, SLIII and FAT, the critical white matter tracts identified in our study. This assumption is further supported by our additional analysis using a probabilistic functional atlas based on the fMRI data of more than 600 participants.[149,150] Our results revealed that MD-weighted lesions are associated with test-level cognition of our patients, as well as their performance in cognition during daily living.

Rich inter- and intra-hemispheric connections are thought to be of crucial importance for the functioning of the extensive MD network, allowing information to be rapidly exchanged and integrated[6], and providing the brain with a mechanism to orchestrate cognition and constantly adapt behaviour to the ongoing conditions.[129] Correspondingly, a recent DTI study in healthy subjects postulated that the SLF and FAT white matter connections might be of central importance for the functioning of the MD network.[130] Our findings confirm and extend this hypothesis in two ways. First, they show that a disconnection of right-hemispheric

SLFII/III/FAT in a lesion model in stroke patients leads to impairments in several cognitive domains, as predicted by the notion of a MD network. Second, they highlight a critical and discrete neuroanatomical locus, i.e., the intersection between SLF II/SLFIII/FAT, as a particularly vulnerable spot within the network.

The role of the IFOF, the white matter tract affected by the second, smaller lesion cluster, is less straightforward to define within the concept of the MD network. So far, IFOF white matter connections seem not be discussed as typical ones in the relatively young literature on the MD network structural connectivity. This opens at least two interim, speculative interpretations. First, considering - on the one hand – the above-mentioned anatomic dissection studies of the IFOF[154] and very recent connectome matrices studies,[162] which show terminations of this tract also in parietal and temporal areas, and – on the other hand – the present results, one may speculate that the IFOF has more to do with the MD network than previously assumed. Second, and mutually not exclusive, the MD network may conceptually and functionally share features with the ventral attention pathways, which have been shown to interconnect several multifunctional areas, and within which the IFOF plays an important connectivity role.[160]

Clinical relevance

Importantly, impaired cognitive performance was not only measurable on a test level, but also in the activities of daily living, which were rated by therapists blind with respect to the study goals. The ecological validation of our results in daily living showed that patients with a lesion involving the intersection of SLF II/SLFIII/FAT and Putamen/IFOF had significantly more severely impaired cognition during daily living than patients without a lesion in this region. More precisely, patients showed more severe difficulties in carrying out simple or complex actions, which are relevant to manage and complete the requirements of daily living.[20,58] This extends earlier findings from dementia and traumatic brain injury patients, namely that the interaction of visuospatial attention, alertness and inhibition is an important determinant to successfully perform the activities of daily living.[15,16]

More generally, our findings confirm that white matter lesions can lead to a breakdown of large-scale brain networks, resulting in several associated cognitive deficits, whereas focal cortical damage provokes more circumscribed patterns of clinical impairment.[21,131-133,148,163] Critically, here we show how damage to a strategic crossroad of white matter pathways can provoke even

larger-scale disruptions of activity in a higher-order MD network, with consequent multiple deficits in different cognitive domains.

Towards an integrative model

We showed that the intersection between SLF II/SLFIII/FAT is particularly crucial. A frontal lesion (Figure 5 red) at this strategical intersection of fronto-frontal tracts (FAT connects the posterior part of the IFG and the pre-SMA;[81-84] Figure 5 in green) and fronto-parietal tracts (SLF II connects the IPL with the frontal eye field [54,85,86] and SLF III connects the IPL and the STG with the IFG;[1,54,64,79,80] Figure 5 in blue), may cause a widespread breakdown of connectivity through the whole right-hemispheric MD network, leading to simultaneous impairment in several cognitive domains such as visuospatial attention, alertness and inhibition, both on a test level as well as in cognition during daily living.

Taken together, previous results and our current findings, which point towards the central importance of disconnection between cortical areas associated with the MD network, strongly suggest that a MD network disorder is an important contributor to the occurrence and persistence of neglect signs. Neglect has indeed been conceptualised as a multicomponent syndrome,[134-136] and many neglect patients do not only suffer from visual attention deficits and impaired alertness, but also present deficits in response inhibition (see for example[13,137,138]). In addition, compensation of neglect signs may critically depend on inhibitory processes,[138,139] which, as suggested by our results, are no longer available after a lesion at the SLFII/SLFIII and FAT intersection. Among other authors, we have indeed previously shown that inhibition failure, with ensuing repetitive behaviour, is influenced by a visual attentional gradient in neglect patients,[13,140,141] and that inhibition failure can even increase neglect severity.[13] Furthermore, rehabilitation studies showed that not only exercising visuospatial attention, but also training alertness and inhibition has a positive effect on neglect recovery.[139,142,143]

Limitations

Our study has some limitations. In our data-driven analysis, the cognitive domains of visuospatial attention, alertness and inhibition as outcome variables were chosen because of their

common link with the activities of daily living[15,16] and their association with right-hemispheric brain lesion.[2,17-19] However, other cognitive domains (e.g., working memory) were not explored. Furthermore, as with any vascular lesion study, stroke lesions are dictated by the vascular architecture of the brain, wherefore critical regions with conserved vascular supply are likely to be underrepresented. Also, we did not include left-hemispheric stroke patients with language deficits such as aphasia. Therefore, future studies may want to investigate the importance of the observed lesion intersection, and its association with deficits in an even broader range of cognitive domains in both hemispheres. Finally, future studies are needed to characterize the potential impact of MD network lesions on the therapeutic effects of conventional therapy approaches, e.g., by investigating the effects of total and partial white matter disconnection (SLF, FAT, IFOF) between MD-related brain areas on therapy outcome.

Conclusion

In conclusion, the present study highlights that visuospatial attention, alertness and inhibition share common grounds on the behavioural as well as the neuroanatomical level. Correlational analyses revealed significant results not only between behavioural outcome variables of the *same* cognitive domains, but also between outcome variables of *different* cognitive domains. Fittingly, lesions critically involving the intersection of white matter connections between parieto-frontal areas (typically SLF II/III, to a lesser extent IFOF) and between preSMA/IFG (FAT), were shown to determine a concurrent functional breakdown in all three domains: visuospatial attention, alertness, and inhibition. Furthermore, patients with more severely impaired test-level cognition and a brain lesions involving the intersection of the above mentioned tracts also presented with significantly more severely impaired cognition during daily living.

This novel and intriguing finding is reminiscent of the MD network model, suggesting that different cognitive operations depend on different collaborators and their interaction, within the same underlying, high-order brain network. Hence, a lesion involving the corresponding intersection would cause a widespread breakdown of connectivity throughout the whole higher-order network, with dramatic consequences on cognitive performance and daily living activities. Such anatomical and cognitive findings, should their influence on clinical outcome be confirmed in longitudinal designs, have the potential to influence rehabilitation approaches.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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Figure legends

Figure 1 Consort flow diagram. Patients' inclusion flow-chart based on the CONSORT 2010 guidelines. 99 patients were assessed for eligibility. Apart from a history of first-ever right-hemispheric stroke, the main inclusion criteria were age above 18 years, normal or corrected-to-normal visual acuity, and being able to undergo an MRI scan. Exclusion criteria were other neurological diseases, major psychiatric diagnoses, and alcohol/drug abuse. 63 patients were allocated to study participation, from which 3 patients withdrawn for personal reasons. In the end, 60 patients completed the assessments and were included in the final analyses.

Figure 2 Behavioural Analyses for the three cognitive domains. **(A)** shows violin wrapping box-and-whisker plots of all z-transformed outcome variables included in the study. The width of the violins represents the proportion of patients with an equivalent z-value. The overall median z-values are indicated by the horizontal white line in each box-and-whisker plot. Each box represents the lower (Q1) to the upper (Q3) quartiles, with whiskers extending from the minimum to the maximum of 1.5 times the interquartile range. The number of available patient data sets for each variable is depicted at the bottom of each violin. Outliers are depicted by grey circles. Blue represents outcome variables typically measuring visuospatial attention (Letter Cancellation Tests=Letter CoC, Line Bisection Test=LB, CoC in the Five-Point Test=FPT CoC, mean gaze position during Free Visual Exploration=FVE), yellow represents outcome variables typically measuring alertness (TAP phasic Alertness=phasic Alert, TAP tonic Alertness=tonic Alert, mean fixation duration during FVE=FVE fix dur, peak saccade velocity during FVE=FVE peak vel), grey represents outcome variables typically measuring inhibition (percentage of perseverative errors in the Five-Point Test=FPT Persev, Go-Nogo paradigm of the FAB=Go-Nogo, errors in the Stroop Interference condition=STROOP, Antisaccade Errors=Antis). **(B)** shows the significant correlations between all 12 variables included in the Principal Component Analysis (PCA). The lines between variables represent significant correlations and their strength: the darker the shade, the stronger the correlation, as represented by the legend on the right-hand side of the panel. **(C)** shows the principal components extracted from outcome variables of the cognitive domains of visuospatial attention, alertness, and inhibition, with factor loadings >.40. The length of the bars represents the loading of each outcome variable onto the extracted factor

components. The components were named as follows: Component 1=*Common Component*; Component 2=*Inhibition/Alertness Component*; Component 3=*Alertness Component*. The figure was illustrated using the R package ggplot2.[144,145]

Figure 3 Neuroanatomical Analysis. (A) depicts the results of the VLSM analysis using the PCA factor values of the *Common Component* (i.e., PCA Component I) as predictive values. The results show two significant lesion clusters (red, with a total volume of 325 voxels). The first and larger cluster (top row) is located within the second branch of the superior longitudinal fasciculus (SLF II, dark blue), the third branch of the superior longitudinal fasciculus (SLF III, light blue), and the Frontal Aslant Tract (FAT, green). The second and smaller cluster (bottom row) is located within the SLF III, the anterior part of the putamen and the Inferior Fronto-Occipital Fasciculus (IFOF, yellow). Patients with right-hemispheric stroke presenting with a lesion within these clusters were significantly more likely to show an impairment in overall cognitive performance in all three considered cognitive domains, as reflected by the lower factor values in the *Common Component* (PCA Component I). **(B)** shows the results of the Disconnectome map analysis for a ROI including all four white matter tracts identified as affected by the previous VLMS analysis, i.e., the SLF II, the SLF III, the FAT, and the IFOF. Patients with right-hemispheric stroke presenting with a lesion within these clusters were significantly more likely to show an impairment in overall cognitive performance in all three considered cognitive domains, as reflected by the lower factor values in the *Common Component*. For both panels, lesion voxels that were a significant predictor for the *Common Component* factor values are depicted in red (significance level $p < .05$, based on the Brunner-Munzel test, FDR-corrected, 4000 permutations). Lesion clusters and white matter tracts are displayed on the MNI152 template in MNI space, as available in MRIcroGL (https://www.nitrc.org/projects/mricrogl/). The axial slices are oriented according to the neurological convention. The position of each slice in MNI space is indicated by numbers at the top of the respective slices. White matter tracts are depicted according to published probabilistic diffusion tensor imaging atlases [53,54] (the probability for voxels to belong to the SLF II (in dark blue), SLF III (in light blue), the FAT (in green), and the IFOF (in yellow) was set at >50%).

Figure 4 Clinical relevance. The relationship between factor values of the *Common Component* (i.e. PCA Component I), the number of tests with clinical significant impairments (top), and cognition during daily living (bottom) is shown. **Top**: a clinical significant impaired behaviour in a larger number of tests measuring visuospatial attention (At, blue), Alertness (Al, yellow), and inhibition (I, grey) was accompanied by lower PCA values. Darker colours indicate a higher number of tests with clinical significant impairment (z<-1.5) in the respective cognitive domain. **Bottom**: Indivual PCA factor values on the *Common Component* (PCA Component I) significantly correlated with measures of cognitve performance in daily living (LIMOS cognition) (p<.001, r=.575). Patients with a lesion involving the intersection of SLF II/III and FAT as well as Putamen/IFOF (red triangles) showed a more severe impairment in cognition during daily living than patients with a lesion not involving the aforementioned VLSM clusters (black circles; t(58)=-2.507, p=.015;). The probability of an individual brain lesion to lay within or outside the VLSM clusters is further depicted by the double-headed arrow. The Figure was illustrated using the R package ggplot2.[144,145]

Figure 5 A putative neuroanatomical model. The putative neuroanatomical model explains how a frontal lesion (red volume), located at the strategical intersection of fronto-frontal and fronto-parietal tracts, can disrupt multiple tracts interconnecting cortical areas within the multiple-demand (MD) network.[6] In particular, the affected white matter fibre tracts are the SLF II (dark blue[79,146]), the SLF III (light blue[79,146]) and the FAT (green[147]). The SLF II and III are generally known to connect parieto-temporal areas to frontal areas (SLF II connects the IPL with the frontal eye field[54,85,86] and SLF III connects the IPL and the STG with the IFG[1,54,64,79,80]). The FAT connects the posterior part of the IFG and the pre-SMA[81-84]. The illustration was created using the HCP1065.2mm template and the implemented automated fibre tracking tool, visualized on the respective T1-image implemented in DSIstudio (Version 2021.12.03; available on http://dsi-studio.labsolver.org/).

Table 1 Overview of neuropsychological tests and oculography paradigms included in the study

	Visuospatial attention	Alertness	Inhibition
Neuropsychological tests	Letter Cancellation Test: spatial distribution (CoC) of cancelled items[27] Line Bisection Test: mean relative deviation from actual midline[28] Five Point Test: spatial distribution (CoC) of drawn designs[29]	TAP tonic alertness: median reaction time[32] TAP phasic alertness: median reaction time[32]	FAB GoNogo: number of errors[35,36] Five Point Test: number of perseverative errors[13] Stroop[38]: Number of errors in the interference test
Oculography paradigms	FVE: Mean gaze position[31]	FVE: Mean fixation duration[41] FVE: Mean peak saccadic velocity[44]	Antisaccade task: Number of errors[39]

FVE=Free Visual Exploration Paradigm; TAP=Test of Attentional Performance; FAB=Frontal Assessment Battery; CoC=Centre of Cancellation.

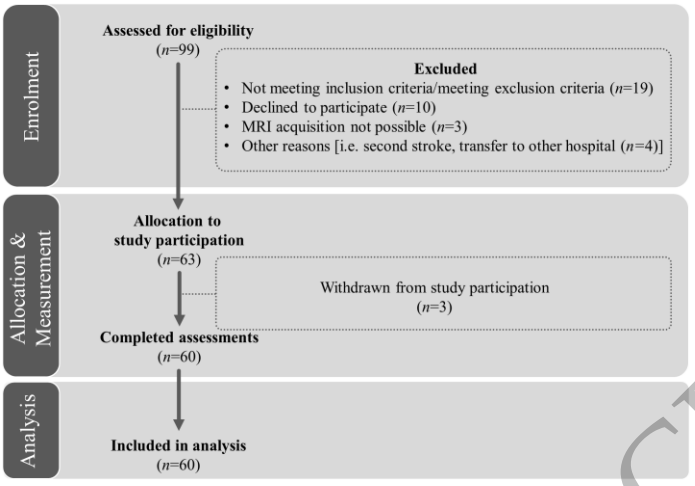

Figure 1
91x63 mm (x DPI)

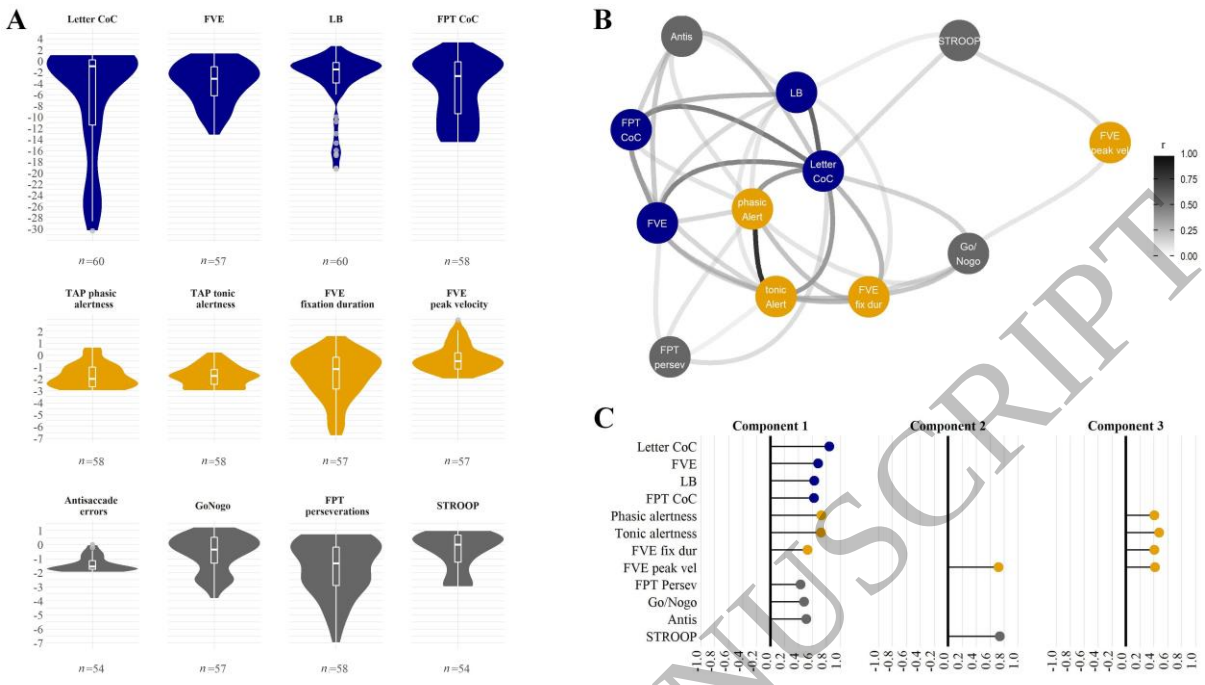

Figure 2
159x89 mm (x DPI)

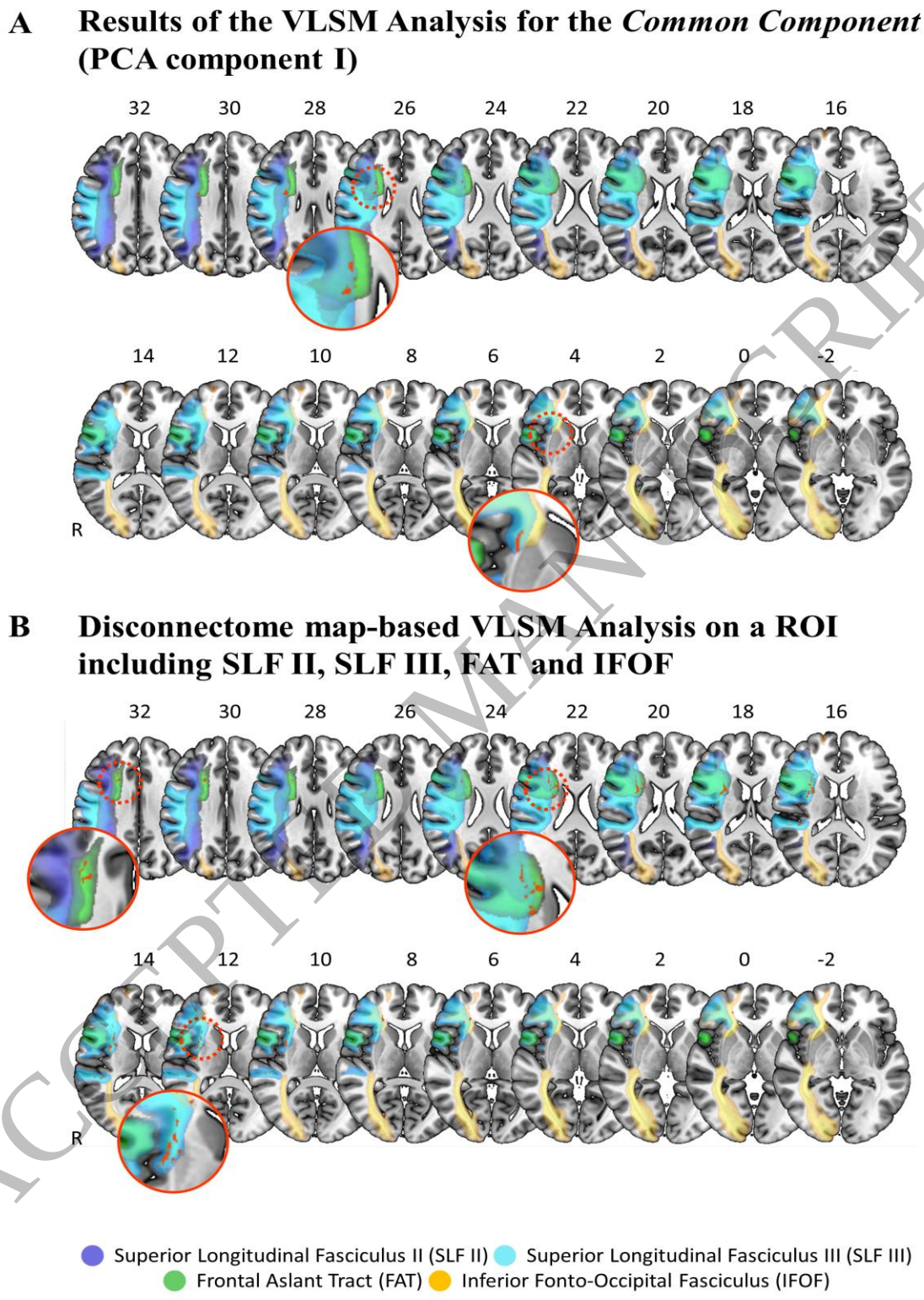

Figure 3
159x230 mm (x DPI)

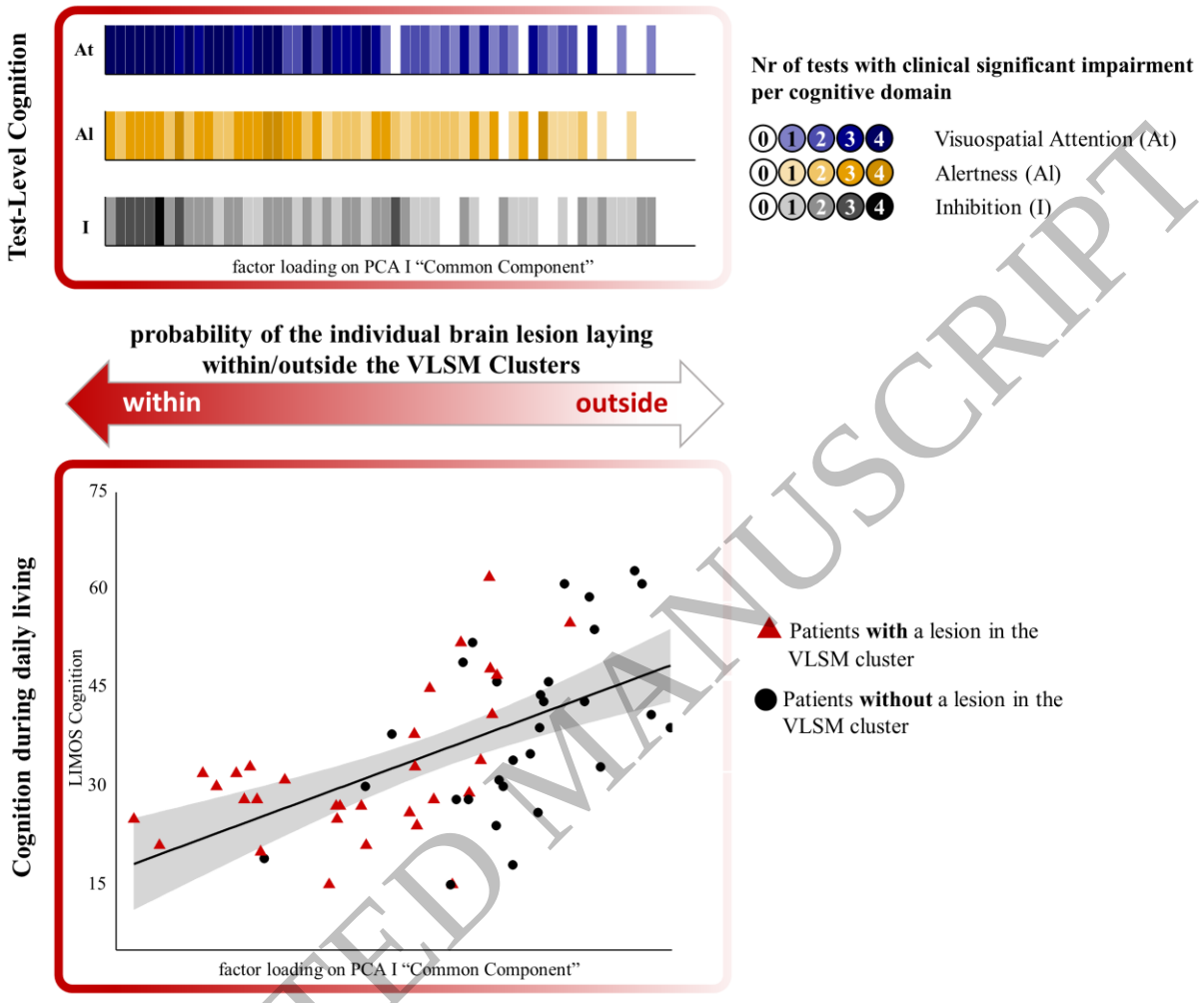

Figure 4
159x133 mm (x DPI)

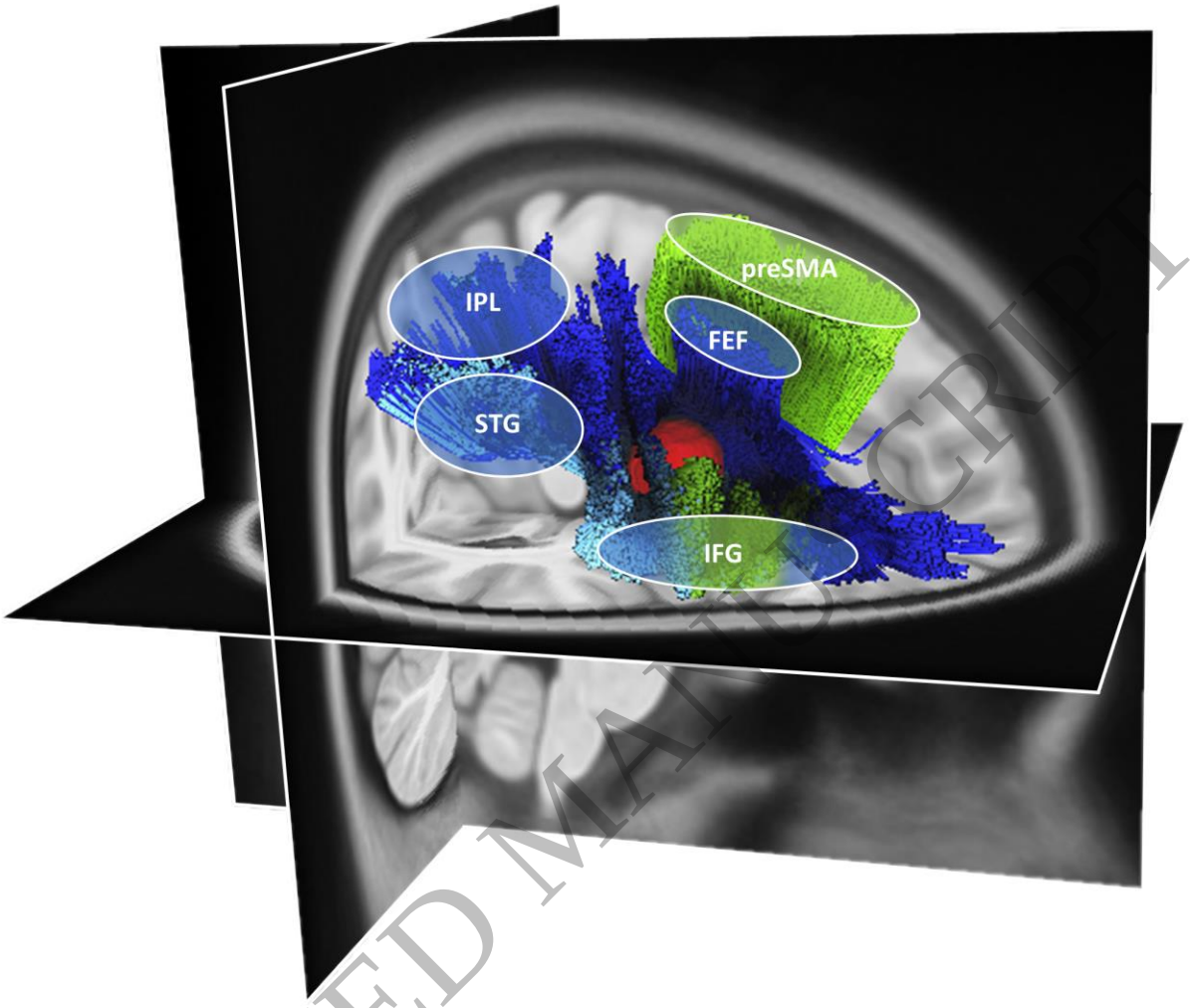

Figure 5
159x135 mm (x DPI)