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► **To cite this version:**

Stefan Smaczny, Christoph Sperber, Stefanie Jung, Korbinian Möller, Hans-Otto Karnath, et al..
Disconnection in a left-hemispheric temporo-parietal network impairs multiplication fact retrieval.
NeuroImage, In press. hal-03925531

HAL Id: hal-03925531

<https://hal.science/hal-03925531>

Submitted on 5 Jan 2023

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1 Disconnection in a left-hemispheric temporo-parietal network impairs 2 multiplication fact retrieval

3

4 Abstract

5 Arithmetic fact retrieval has been suggested to recruit a left-lateralized network comprising
6 perisylvian language areas, parietal areas such as the angular gyrus (AG), and non-neocortical
7 structures such as the hippocampus. However, the underlying white matter connectivity of
8 these areas has not been evaluated systematically so far.

9 Using simple multiplication problems, we evaluated how disconnections in parietal brain areas
10 affected arithmetic fact retrieval following stroke. We derived disconnectivity measures by
11 jointly considering data from n=73 patients with acute unilateral lesions in either hemisphere
12 and a white-matter tractography atlas (HCP-842) using the Lesion Quantification Toolbox
13 (LQT). Whole-brain voxel-based analysis indicated a left-hemispheric cluster of white matter
14 fibers connecting the AG and superior temporal areas to be associated with a fact retrieval
15 deficit. Subsequent analyses of direct grey-to-grey matter disconnections revealed that
16 disconnections of additional left-hemispheric areas (e.g., between the superior temporal gyrus
17 and parietal areas) were significantly associated with the observed fact retrieval deficit.

18 Results imply that disconnections of parietal areas (i.e., the AG) with language-related areas
19 (i.e., superior and middle temporal gyri) seem specifically detrimental to arithmetic fact
20 retrieval. This suggests that arithmetic fact retrieval recruits a widespread left-hemispheric
21 network and emphasizes the relevance of white matter connectivity for number processing.

22 Keywords

23 Disconnectome, VLSM, Arithmetic Fact Retrieval, Lesion Mapping, Connectivity

24

25 Highlights

- 26 • Examination of the effect of disconnectivity following stroke on multiplication
- 27 • WM between AG and superior temporal areas was associated with worse multiplication
- 28 • Disconnections in the arithmetic fact retrieval network led to worse multiplication
- 29 • White matter disconnectivity needs more examination in numerical cognition research

30

31 1. Introduction

32 The dominating view in numerical cognition is that arithmetic facts such as multiplication
33 tables are stored in and retrieved from long-term memory in a verbal format (e.g., Dehaene et
34 al., 2003; Delazer et al., 2003; Grabner et al., 2009). The triple code model (Dehaene & Cohen,
35 1995; 1997; Dehaene et al., 2003), which has been remarkably successful in providing a
36 theoretical framework for neuroimaging research on numerical cognition, posits that the
37 retrieval of arithmetic facts recruits areas also involved in language processing such as left-
38 hemispheric perisylvian areas and the left angular gyrus (AG). In contrast, the manipulation of
39 numerical content during magnitude-manipulation-based calculation (e.g., addition,
40 subtraction) has been associated with a fronto-parietal network for number (magnitude)
41 processing centered around the intraparietal sulcus (IPS; e.g., Dehaene et al., 2003; for a meta-
42 analysis see Arsalidou & Taylor, 2011). This network has recently been coined the 'math-
43 responsive network' (Amalric & Dehaene, 2017; 2019).

44 The retrieval of rote learned arithmetic facts has been assumed to be processed multi-modularly
45 and distributed within a left-lateralized language network, including inferior frontal gyrus
46 (IFG; Delazer et al., 2003), middle and superior temporal gyri (MTG/STG), supramarginal
47 gyrus (SMG), intraparietal sulcus (IPS, Salillas et al, 2011); angular gyrus (AG; e.g., Dehaene
48 et al., 2003; Delazer et al., 2003; Grabner et al., 2009a; 2009b), and hippocampus (e.g.,
49 Bloechle et al., 2016; Delazer et al., 2019; Klein et al., 2016; 2019). However, it is important
50 to note that recent evidence in healthy participants and from neurosurgery in tumor patients has
51 also pointed to the role of right hemispheric structures in tasks reliant on arithmetic fact
52 retrieval (Arcara et al., 2021; Salillas et al, 2021; Semenza et al., 2017). However, the exact
53 role of some of these areas is still debated. On the one hand, several case studies reported
54 patients with a preserved AG who presented selective deficits for arithmetic fact retrieval (as
55 measured by a multiplication task, Cohen et al., 2000; Dehaene & Cohen, 1997; Van Harskamp
56 et al., 2005). On the other hand, it has been criticized that the interaction of several of these

57 areas, which are activated during arithmetic fact retrieval, may not be specific to arithmetic fact
58 retrieval. For instance, IFG, STG, and SMG are typically also involved in phonological
59 decoding during language processing (Prado et al., 2011; Vigneau et al., 2006; for a review,
60 see Price, 2012). Similarly, modulation of AG (de)activation, observed for arithmetic fact
61 retrieval, was also found for non-mathematical content (Ischebeck et al., 2007; Zamarian et al.,
62 2009). In a single-case training study, Zaunmueller et al. (2010) examined the fMRI signal in
63 a patient with aphasia, who also showed deficits in multiplication fact retrieval. For untrained
64 problems, the patient demonstrated strong activations in left prefrontal areas and the right
65 posterior AG. This observation corroborates the verbally reported use of back-up strategies,
66 such as the recital of a multiplication row. For trained problems, activation was stronger in a
67 more anterior segment of the right AG, whereby the patient had reported using more retrieval-
68 based strategies. A similar example is provided by a single case reported by Delazer and Benke
69 (1997): After the resection of a left parietal tumor, the patient was no longer capable of
70 understanding arithmetic on a conceptual level, yet was able to produce the correct answer to
71 several arithmetic tasks due to memorised fact knowledge. Therefore, it appears likely that
72 (sub)processes of arithmetic fact retrieval are related to phonological language processing.

73 However, such an association between arithmetic fact retrieval and language processing is still
74 debated. Amalric and Dehaene (2016, 2017, 2019) suggested that simple, overlearned
75 arithmetic facts might be processed independently of left-hemispheric language areas.
76 Evidence for a dissociation between arithmetic and non-arithmetic fact storage was provided
77 by a case study of semantic dementia (Zamarian et al., 2006). The patient's semantic fact
78 knowledge remained intact, while their non-arithmetic semantic knowledge did not. In
79 particular, the authors proposed that procedure-based calculation and overlearned arithmetic
80 facts are processed within the bilateral fronto-parietal 'math-responsive' network.

81 However, the empirical evidence concerning this question is still inconsistent on whether
82 arithmetic fact retrieval and language processes recruit overlapping cortical circuits. There
83 seems to be a consensus that arithmetic fact retrieval is processed multi-modularly and
84 distributed in distinct brain regions. Therefore, it is critical to consider network characteristics
85 such as connectivity between distant brain regions and subnetworks.

86 Studies examining white matter correlates in children point to the importance of fronto-parietal
87 connections in numerical and mathematical cognition (see Matejko & Ansari, 2015; Peters &
88 de Smedt for reviews). For arithmetic fact retrieval in children, Van Beek et al. (2013) found

89 that fractional anisotropy, a measure of white matter integrity, correlated with multiplication
90 and addition in the left anterior segment of the arcuate fasciculus. Moreover, when controlling
91 for different types of reading measures, this association disappeared. This further corroborates
92 that arithmetic fact retrieval of multiplication relies heavily on phonological processing. Klein
93 et al. (2016) provided further evidence for white matter connectivity underlying arithmetic fact
94 retrieval using probabilistic fiber tracking in healthy adults. The authors showed that parietal
95 areas are connected with frontal areas dorsally via the cingulate bundle and ventrally via the
96 extreme/external capsule system and temporal areas via the inferior longitudinal fascicle. The
97 importance of the integrity of such a network architecture for fact retrieval has already been
98 highlighted in some studies: For instance, in a re-evaluation of a single case reported by
99 Zaubmueller et al. (2009), Klein et al. (2013b) found that the lesion was limited to the basal
100 ganglia region (and did not involve the AG) but nevertheless led to disruption of white matter
101 fibers connecting frontal areas with the AG. Based on this, the authors suggested that the patient
102 could not retrieve arithmetic facts because of disconnection within their retrieval network and
103 not because of actual grey matter damage in cortex areas associated with fact retrieval. In this
104 vein, Mihulowicz et al. (2014) conducted a voxel-based lesion behaviour mapping study
105 (VLBM). VLBM analyses the association of voxel-wise lesion status (lesioned or not lesioned)
106 with a given behavioural variable to map the neural correlates of neuropsychological pathology
107 and the functional anatomy of the human brain (Rorden & Karnath, 2004). For each voxel, the
108 relation between anatomical pathology and behavioural pathology is statistically tested and
109 corrected for multiple comparisons. They observed a significant association of lesions in the
110 dorsal pathway (i.e., parts of the superior lateral fasciculus) with arithmetic fact retrieval.

111 Only recently, lesion-disconnectome mapping has brought forward the possibility to more
112 closely examine the role of white matter network disruption of brain lesions in post-stroke
113 cognitive deficits. In particular, it allows for an indirect assessment of lesion-induced
114 disconnections by reference to healthy connectome data (e.g., Griffis et al., 2019). Information
115 about a patient's structural lesions is incorporated into a connectome of healthy subjects to
116 estimate potential disconnection. In the current study, we evaluated brain disconnections
117 associated with low performance in arithmetic fact retrieval in acute left- and right-hemisphere
118 stroke patients at the group level. We expected that white matter disconnection of voxels within
119 the left-hemispheric arithmetic fact retrieval network, including, among others, AG and MTG,
120 should be associated with low performance in arithmetic fact retrieval. In a subsequent analysis,
121 we specifically evaluated disconnections between grey matter regions. That is, over the entire

122 brain, we examined which direct grey matter-to-grey matter disconnections are significantly
123 associated with a low performance in arithmetic fact retrieval. Again, we expect to find that
124 disconnections between grey matter regions involved in the arithmetic fact network are
125 associated with a low behavioural performance. Therefore, the first analysis should provide
126 white matter areas whose level of disconnection is associated with low performance, while the
127 second analysis should provide specific grey matter-to-grey matter disconnections associated
128 with low performance.

129

130 2. Methods

131 2.1 Participants

132 We used the existing patient data set from Mihulowicz et al. (2014) and added 28 new patients
133 for the present analyses. In total, 73 native German-speaking acute stroke patients participated
134 in the study. All of them were patients consecutively admitted to the Center of Neurology at
135 Tuebingen University Hospital over 33 months (cf. Mihulowicz et al., 2014) plus another 18
136 months, whereby the experimental tasks and procedure were identical in both data acquisition
137 phases. Among these, 38 patients presented with left hemisphere damage (LHD) and 35
138 patients with right hemisphere damage (RHD). Patients were only included when they
139 presented an MR- or CT-documented cerebral stroke, not more than 14 days post-onset. We
140 did not include patients with previous lesions, other neurological or psychiatric diseases, or
141 white matter alterations. Patients or their relatives gave their informed consent to participate in
142 the study. The study followed the ethical standards in the Declaration of Helsinki (Version
143 2013) and was approved by the local ethics committee (Vote 82/2018 BO2). Clinical and
144 demographic data for the whole group of 73 patients are given in Table 1; an illustration of the
145 lesion overlap of all participants can be seen in Figure 1.

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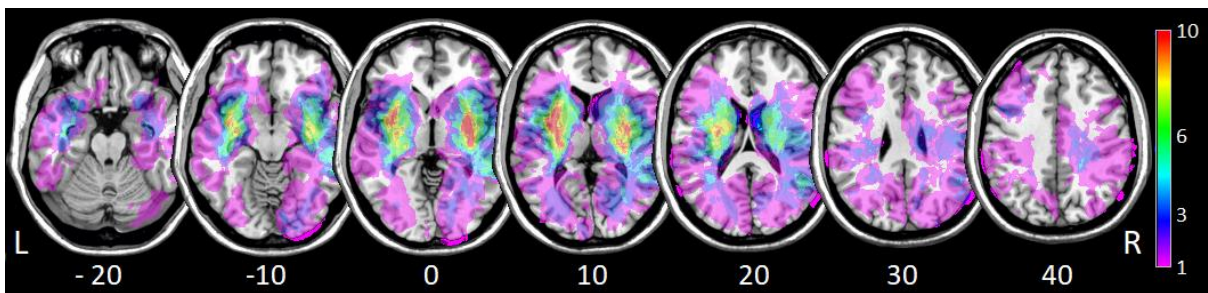
Table 1 | Demographic and clinical data of all LHD and RHD patients

	LHD	RHD
<i>N</i>	38	35
Sex	19F, 19M	18F, 17M

Age (years)	Mean (SD)	63.05 (14.22)	63.38 (15.37)
Stroke type	Ischemic / Hemorrhage	32 / 6	28 / 9
Interval lesion onset to examination (days)	Mean (SD)	4.8 (2.5)	4.4 (2.3)
Interval lesion onset to imaging (days)	Mean (SD)	2.7 (2.6)	2.7 (3.2)
Education (years)	Mean (SD)	11.27 (4.36)	11.14 (4.43)
Contralateral paresis	% present	52.63	65.71
Visual field deficit	% present	13.16	11.43
Aphasia	% present	42.10	-
Spatial Neglect	% present	-	13.89

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2.2 Procedure

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Patients were investigated in sitting position. The entire experiment took about one hour and was completed in one session for most patients. For some, further sessions were needed due to clinical examinations or because they needed a break. For the multiplication task, patients responded verbally and in written form when the former was impossible.

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We ensured that all patients were able to follow the task instructions. In particular, we tested receptive and expressive language abilities in LHD patients. For *language comprehension*, we used the 'Colour-Figure' subtest from the German adaptation of the Aphasia Check List (ACL; Kalbe et al., 2005). In this task, patients were presented with different coloured shapes. They

165 were asked to touch them in different syntactical complexities (e.g., “touch the small blue
166 triangle after touching the large blue triangle”). We applied the 'Picture naming task' of the
167 Aachener Aphasia-Bedside Test (AABT; Biniek et al., 1992) to assess language production.
168 Patients were presented with drawings of everyday objects and were asked to name them.

169 We also tested patients with RHD for *spatial neglect*. The neglect test comprised the 'Letter
170 Cancellation Task' (Weintraub & Mesulam, 1985), the 'Bells test' (Gauthier et al., 1989), as
171 well as a copying task (Johannsen & Karnath, 2004). In the cancellation tasks, patients were
172 presented with arrays of letters and had to cross out 'A's (Letter cancellation) or dark objects,
173 such as keys, apples, or bells. Patients had to cross out all bells (Bells cancellation). We
174 calculated the Centre of Cancellation (CoC) for the two cancellation tasks, using the procedure
175 and cut-off scores for diagnosing spatial neglect described by Rorden and Karnath (2010). In
176 the copying task, patients were asked to copy a complex multi-object scene consisting of four
177 figures (a fence, a car, a house, and a tree), with two of them located in each half of the
178 horizontally oriented sheet of paper. The omission of at least one of the contralateral features
179 of each figure was scored as 1. The omission of each whole figure was scored as 2. One
180 additional point was given when contralaterally located figures were drawn on the ipsilesional
181 side of the paper sheet. The maximum score was 8. A score higher than 1 (i.e., > 12.5%
182 omissions) was taken to indicate neglect. Patients were diagnosed with spatial neglect if they
183 scored above the respective cut-off as per the manual in at least 2 out of 3 tests.

184 Visual field deficits were assessed in all patients via the standard neurological confrontational
185 procedure. Here, the experimenter stands centrally in front of the patient and instructs them to
186 focus on their nose. Then, the experimenter wiggles their finger in the left or right visual field
187 of the patient at different heights. The patient is instructed to report whether the finger moves
188 or not. Table 1 presents all clinical data.

189

190 2.3 Stimuli

191 As part of our battery, we evaluated patients' arithmetic fact retrieval through a single-digit
192 multiplication production task (i.e., 42 items from arithmetical tables up to 9×9), included in
193 the standardized neuropsychological Number Processing and Calculation Battery (NPC;
194 Delazer et al., 2003). Each multiplication problem was presented on a separate A4 sheet (black
195 digits printed on white paper, digit height: 7 mm). Sheets were aligned centrally on a table in
196 front of the patient. According to the standardized NPC procedure, testing was stopped after

197 five consecutive incorrect or missing responses, and no time limit was imposed. However,
198 responses lasting longer than 10 seconds were rated as incorrect, as this implies a failure in
199 instant fact retrieval. Self-corrections were allowed. In addition and subtraction, 67 out of 73
200 patients made a maximum of two errors, which is non-pathological (see supplementary table
201 S1). This lack of behavioural variance made lesion analysis unviable specifically for addition
202 and subtraction.

203 One aphasic LHD patient could not solve the single-digit multiplication production task orally
204 or in writing, while he could solve 24 of 25 addition tasks correctly in verbal form (over the
205 cutoff time of 10 seconds). In this patient, we applied a multiple-choice version of the
206 multiplication task also provided in the NPC to determine a core deficit in multiplication
207 processing rather than a language difficulty. The multiple-choice version tested the same
208 multiplication problems (e.g., 6 x 7) but provided four solution probes (i.e., correct solution,
209 42; one operand error, e.g., 45, one table error, e.g., 49, and one close-miss error, e.g., 39). The
210 patient showed deficits in the multiple-choice version. Accordingly, his score of 0 in the
211 multiplication production task was included in the data analysis.

212

213 2.4 Lesion Analysis

214 We used diffusion-weighted MRI images taken within 48h after stroke (Weber et al., 2000) or
215 else T2-weighted fluid-attenuated inverse-recovery (FLAIR) images (Brant-Zawadzki et al.,
216 1996; Noguchi et al., 1997; Ricci et al., 1999; Schaefer et al., 2002). In case MR imaging was
217 not conducted, CT images were used (MRI: $N=29$; CT: $N=44$). When several imaging data sets
218 existed for an individual patient, we used the session closest in time to behavioral testing
219 showing a clear demarcation. Lesion borders were marked semi-automatically using the
220 'Clusterize Toolbox' (de Haan et al., 2015). Then, both the anatomical scan and the lesion map
221 were normalized into stereotaxic space using the 'Clinical Toolbox' (Rorden et al., 2012;
222 www.mccauslandcenter.sc.edu/CRNL/clinical-toolbox) implemented in SPM12
223 (www.fil.ion.ucl.ac.uk/spm).

224

225 2.5 Whole-brain disconnectivity mapping

226 We created individual white matter disconnectivity topographies for each patient. These
227 topographies indicate the proportion of disconnected fibers for each white matter voxel in the

228 brain imaging space running through this voxel. Thereby, it allows a topographical assessment
229 of a lesion's impact on brain connectivity as a whole. To this end, we applied the Lesion
230 Quantification Toolkit (LQT; Griffis et al., 2021). The LQT utilizes a tract-wise connectome
231 atlas and embeds the patient's lesion map into it. The toolkit identifies all fiber streamlines that
232 intersect with the lesion and maps connectome-wide disconnection induced by the lesion. In
233 other words, each voxel value corresponds to the percentage of all streamlines within this voxel
234 that are expected to be disconnected by the lesion. We used the LQT's standard HCP-842 atlas
235 (Yeh et al., 2018) for atlas-based tractography, keeping the default parameter setting as
236 suggested in the LQT manual.

237 Subsequently, we further analyzed these continuous disconnectivity maps using mass-
238 univariate General Linear Models in 'NiiStat' (<https://github.com/neurolabusc/NiiStat>). In this
239 analysis, the predictor variable was the previously mentioned percentage value of disconnected
240 streamlines of a voxel, while the outcome variable was the multiplication score. Only voxels
241 with a disconnection in at least five patients were considered in the analysis. Tests were
242 performed one-sided at $p < 0.05$ and corrected for family-wise errors. The family-wise error rate
243 was corrected using 5000 permutations with maximum statistic permutation (Nichols &
244 Holmes, 2002). This disconnectivity topography mapping thus identified voxels for which
245 disconnection is associated with low performance in multiplication. As the patient with a
246 multiplication score of 0 may have affected the results disproportionately, we reran the analyses
247 excluding this patient.

248

249 2.6 Whole-brain Bayesian disconnectivity mapping

250 Using the aforementioned disconnection maps, we used custom code written in R (R Core
251 Team, 2022) to correlate the voxel-wise percentage of disconnected streamlines with the
252 multiplication score and to derive a Bayes Factor for each voxel. The Bayes factor describes
253 the relative difference in evidence for H_1 compared to H_0 . Thus, it enables the quantification
254 of evidence for or even against an effect independently of an arbitrary cut-off such as the p-
255 value, transparently highlighting limitations in statistical power when evidence for neither
256 hypothesis is strong. Again, only voxels with a disconnection in at least five patients were
257 considered. This second disconnectivity topography thus quantified the evidence for each voxel
258 disconnection's association with low performance in multiplication. As above, we ran the
259 analysis twice: Once including and once excluding the patient with 0 points in the
260 multiplication task.

261

262 2.7 Region-to-region disconnectivity

263 We additionally analyzed parcel-wise disconnectivity as provided by the LQT. This procedure
264 allowed us to identify which direct disconnections between two grey matter regions are
265 significantly associated with low performance in the multiplication task. We created a
266 structural connectivity matrix by combining the provided tractography atlas and the
267 Brainnetome Atlas (BN-246, Fan et al., 2016) as our grey matter parcellation atlas. The BN-
268 246 is multi-modally derived, contains 210 cortical and 36 subcortical subregions, and was
269 developed specifically for connectivity analyses. The number of streamlines disconnected by
270 the lesion map between each pair of parcels was converted to a percentage of disconnected
271 streamlines, resulting in symmetric 246-by-246 disconnectivity matrices. Each value in this
272 matrix denotes the percentage of disconnected streamlines between two given grey matter
273 areas. We subjected these matrices to a mass-univariate analysis to identify associations
274 between disconnection and low performance in multiplication using custom scripting in
275 MATLAB R2020a. Following the strategy of the topographical analysis of brain-wide
276 disconnectivity maps described above, we employed mass-univariate general linear models
277 with a family-wise error correction by maximum statistic permutation (Nichols & Holmes,
278 2002).

279 We loaded disconnection matrices into MATLAB and removed the diagonal and redundant
280 elements below it. Many ROI-to-ROI disconnections were rarely or never present in the data,
281 likely either because the sample's lesion anatomy did not include damage to the connection or
282 because the connection was physiologically non-existent. Therefore, we identified the sum of
283 all patients with a disconnection present (i.e., a disconnection score > 0) for each ROI-to-ROI
284 connection. We removed all connections affected in less than 15 patients from the analysis,
285 reducing the final set of analyzed connections to 955 (see Sperber et al., 2022). We then
286 computed a general linear model for each ROI-to-ROI connection with the independent
287 variable disconnectivity score and the dependent variable multiplication performance. Then,
288 maximum statistic permutation with 50,000 permutations was employed on permuted
289 behavioral data and the original disconnection data with the same analysis strategy to assess
290 the distribution of maximum statistics under the null hypothesis. We obtained a one-sided,
291 corrected threshold for statistical significance at $p < 0.05$ by identifying the 95th percentile of
292 permutation-derived maximum statistics. As above, the patient with a multiplication score of
293 0 may have affected the results disproportionately. Therefore, we also analysed the data
294 excluding this patient.

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2.8 Region-to-Region disconnectivity using Bayesian hypothesis testing

To quantify the evidence for the association of disconnections with multiplication performance (see Keyzers et al., 2020), we used the identical method as in the previous section, except that we used a correlation with Bayesian hypothesis testing instead of a frequentist GLM with permutation correction. We used the approach and code provided by Wetzels and Wagenmakers (2012). This analysis enables the continuous quantification of evidence for or against an association of disconnection with multiplication performance. We also analysed the data excluding the patient with 0 points.

2.9 Data availability statement

Online materials, including all analysis scripts, descriptive data, and resulting topographies, are publicly available at <http://dx.doi.org/10.17632/yjkr647mzb.1>. The clinical datasets analyzed in the current study are not publicly available due to the data protection agreement approved by the local ethics committee and signed by the participants.

3. Results

3.1 Behavioral measures

Table 2 summarizes the behavioral results of the multiplication task. Items involving '0' or '1' as operands (n=6) were excluded from the analysis because they address rule-based processing (McCloskey et al., 1991). While the analysis used continuous values, five patients in the RHD group performed below the typical cut-off in the multiplication task; in the LHD group, ten patients did so, including one aphasic patient who could not respond to the multiplication task orally or in writing. As that patient also showed deficits in the aforementioned multiple-choice task but could carry out some other tasks, they were included in the analysis with 0 points for the current task.

Table 2 | Raw scores (number of items solved correctly) observed for the two patient groups in the multiplication task

LHD (n = 38)

RHD (n = 35)

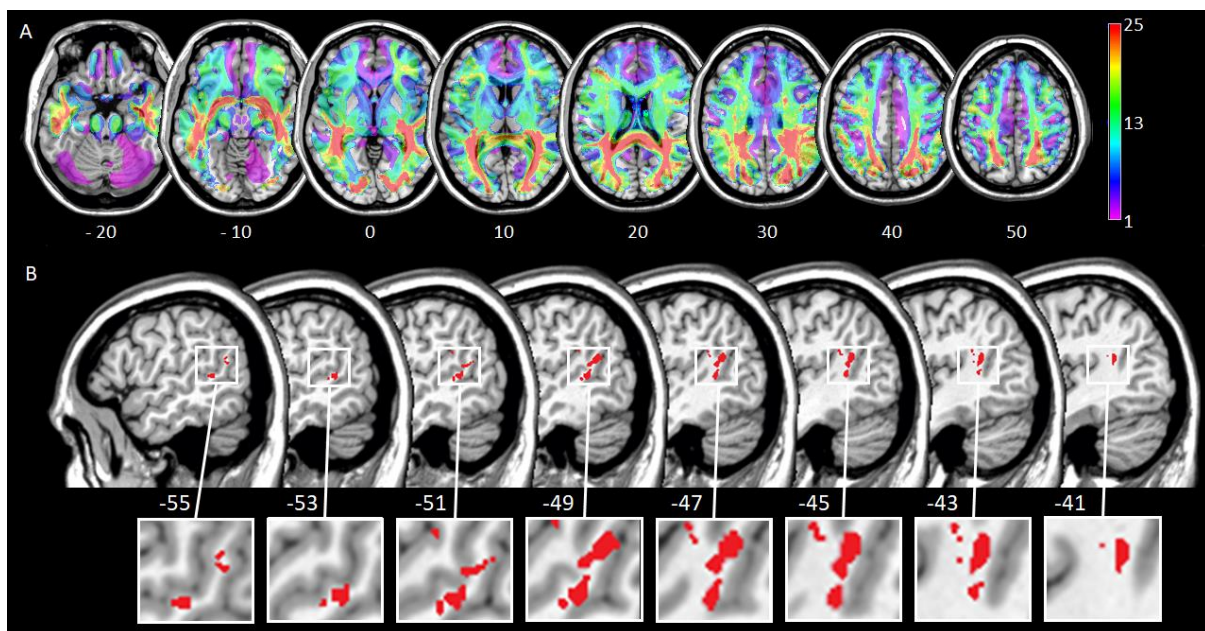
	Items	Mean	Median	SD	Range	Mean	Median	SD	Range
Multiplication	36	29.73	33	8.91	0-36	32.92	34	4.14	21-36

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323 3.2 Brain-wide disconnectivity mapping

324 Figure 2 (Panel A) illustrates the average percentage of lesion-induced disconnection for all 73
 325 patients. Low single-digit multiplication performance was significantly associated with the
 326 disconnection of a single cluster around $x = (-59; -40)$, $y = (-57; -39)$, and $z = (3; 22)$, affecting
 327 areas defined by the HCP-842 as the left arcuate fasciculus, temporo-pontine tract, and U-fibers
 328 between the AG and superior temporal areas (see Figure 2, Panel B).

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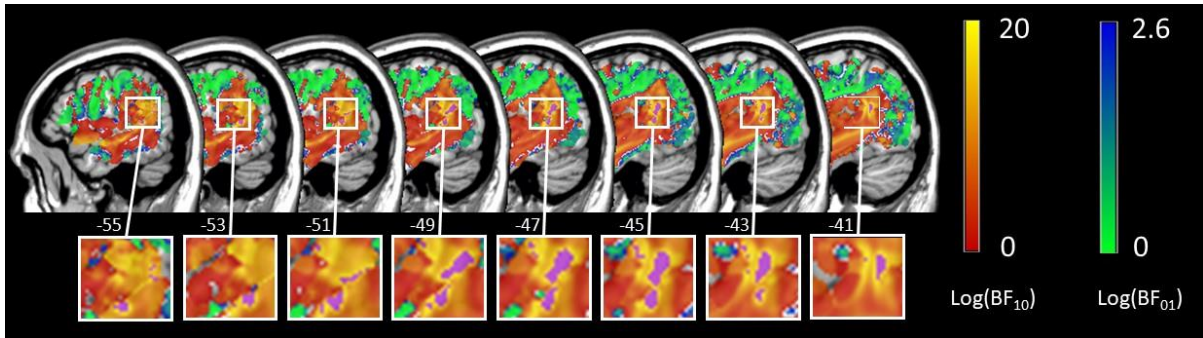


330

331 **FIGURE 2 | Frequentist disconnectivity mapping.** (A) The percentage of fiber disconnection, as
 332 indicated by the average reduction in streamline density, is color-coded from 1 (pink) to 25 (red),
 333 whereby the maximum value in a voxel was 36. A higher number indicates a higher percentage of fiber
 334 disconnection. Topographies can be viewed in the online data. The vertical z coordinate of standardized
 335 MNI space is given below each slice. (B) Sagittal view of the left hemisphere. Statistical voxel-wise
 336 lesion-behavior mapping (VLBM) analyses using mass-univariate general linear models in
 337 multiplication. Plotted are voxels that survived permutation-based FWE correction at $p < 0.05$. The
 338 sagittal x coordinate of standardized MNI space is given below each slice.

339

340 As one patient had a multiplication score of 0, their response may have influenced the results
 341 disproportionately. When this patient was excluded from the analysis, no voxels reached
 342 significance. To quantify the evidence of an effect in those voxels independently of a
 343 significance threshold, we also carried out the same analysis using Bayesian null hypothesis
 344 testing (BNHT) once with, and once without the outlying patient.

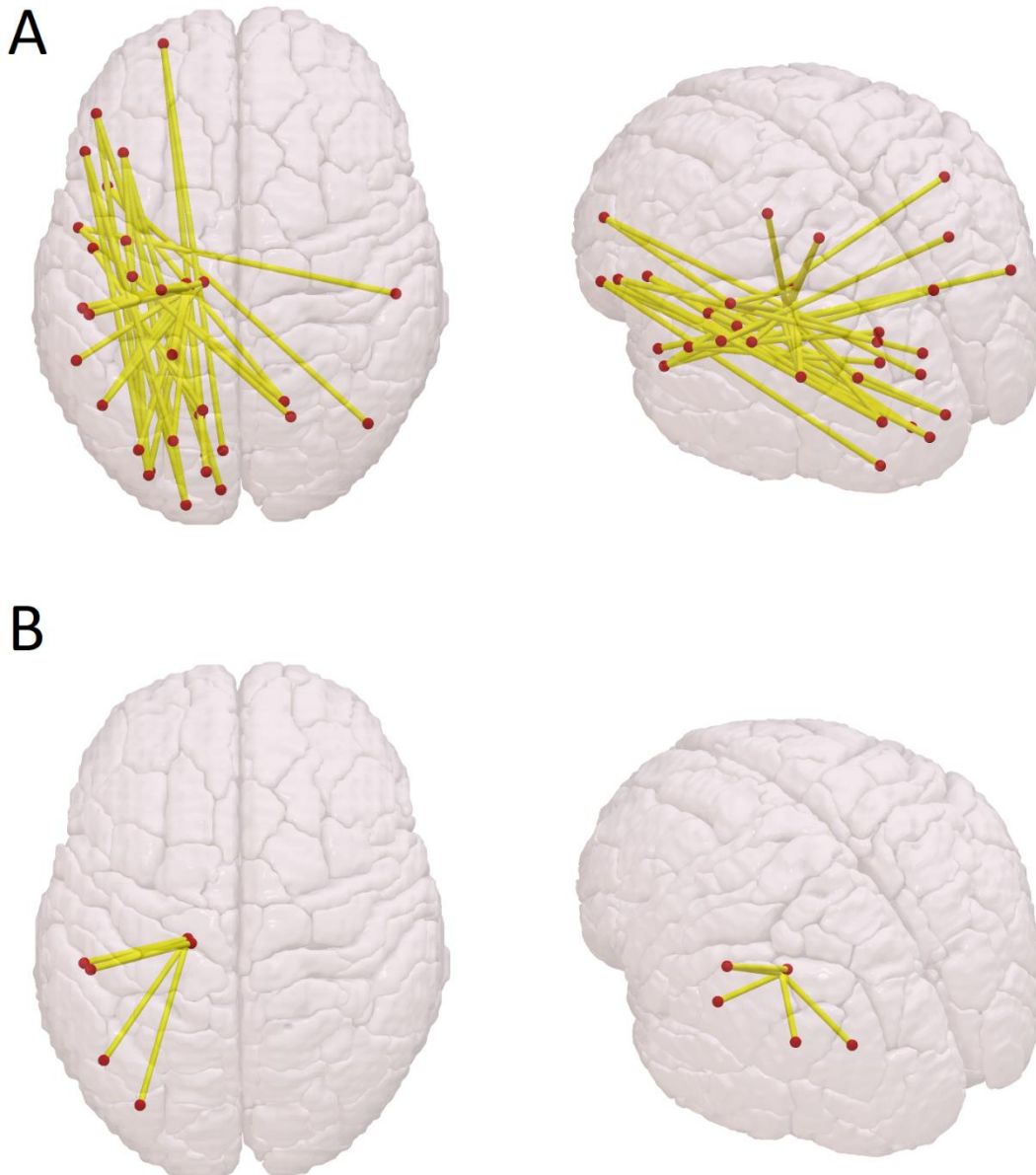


345
 346 **FIGURE 3 | Bayesian disconnectivity mapping.** Sagittal view of the left hemisphere. The heatmap
 347 denotes log-Bayes factors of correlations between voxel-wise disconnection value and multiplication
 348 score, as some values were so large that MRICron could not display them. Voxels marked in a red-to-
 349 yellow manner had BFs indicating evidence for their association with multiplication score, while voxels
 350 marked in green-to-blue indicate evidence for no association with multiplication score. Purple indicates
 351 the voxels that were significant following the frequentist analysis (see Figure 2). The sagittal x-
 352 coordinate of standardized MNI space is given below each slice. Note that $\log(1) = 0$, therefore if a
 353 voxel has value 0, the BF for this voxel = 1 (i.e., when the evidence for H1 and H0 are equal).

354
 355 Figure 3 shows the results of the brain-wide disconnectivity mapping using BNHT while
 356 including all patients. The largest BFs were found in nearly the identical voxels as in the
 357 frequentist analysis, in a cluster around the left AG (see panel B). Additionally, the continuous
 358 mapping of BFs also uncovered a cluster ranging from the AG down to anterior segments of
 359 the STG. When excluding the patient with zero points, the general pattern of results remained
 360 the same, only that BFs were smaller (see Appendix A).

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3.3 Region-to-region disconnectivity



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367 **Figure 5 | Parcel-to-parcel disconnections following the region-to-region disconnectivity analysis.**

368 The image presents the disconnections significantly associated with a low multiplication performance
 369 following the permutation-based GLM (A) with all patients and (B) when excluding the patient with
 370 zero points.

371

372 Mapping multiplication score to ROI-to-ROI disconnectivity using general linear models
 373 identified 41 connections significant at $p < 0.05$ (see Figure 5 (Panel A), Table 3). The
 374 disconnectome revealed several regions that stood out due to several disconnections associated
 375 with low performance in multiplication. A hub-like structure was found for the left thalamus,
 376 with 18 disconnections mainly to the left inferior and superior parietal lobules, including PGa
 377 of the angular gyrus. Furthermore, 14 disconnections between the left IFG and the medioventral
 378 occipital cortex as well as the left lateral occipital cortex were also associated significantly with

379 poorer multiplication scores. Finally, further 5 disconnections from the left STG to the right
380 inferior and superior parietal lobules (IPL, SPL), as well as to the right precuneus, were
381 significant. When excluding the patient with zero points in the multiplication task, only 5
382 disconnections were left over. Four were from the left sensory thalamus to areas PGp, PFt,
383 PGa, PFop of the left IPL and one was from the left posterior parietal thalamus to the left PFt
384 (Figure 5, Panel B).

385

386

Side	Lobe	Gyrus	Name	Name	Gyrus	Lobe	Side			
Left	F	IFG	A44op, opercular area 44	OPC, occipital polar cortex	LOccC	O	Left			
			A44op, opercular area 44	iOccG, inferior occipital gyrus			Left			
			A44op, opercular area 44	msOccG, medial superior occipital gyrus			Left			
			A44op, opercular area 44	lsOccG, lateral superior occipital gyrus			Left			
			A44op, opercular area 44	mOccG, middle occipital gyrus			Left			
			A45c, caudal area 45	OPC, occipital polar cortex			Left			
			A45c, caudal area 45	msOccG, medial superior occipital gyrus			Left			
			A45c, caudal area 45	lsOccG, lateral superior occipital gyrus			Left			
			A45c, caudal area 45	mOccG, middle occipital gyrus			Left			
			A45r, rostral area 45	iOccG, inferior occipital gyrus			Left			
			A44op, opercular area 44	cCunG, caudal cuneus gyrus			MvOccC	Left		
			A44op, opercular area 44	cLinG, caudal lingual gyrus				Left		
			A45r, rostral area 45	cCunG, caudal cuneus gyrus			Left			
			A45r, rostral area 45	cLinG, caudal lingual gyrus			Left			
			MFG	A10l, lateral area10			cLinG, caudal lingual gyrus	Left		
				A10l, lateral area10			rCunG, rostral cuneus gyrus	Left		
			PrcG	A4ul, area 4upper limb region			PPtha, posterior parietal Thal	Thal	S	Left
				A4ul, area 4upper limb region			IPFtha, lateral pre-frontal Thal			Left
	I	IG	dla, dorsal agranular insula	OPC, occipital polar cortex	LOccC	O	Left			
			dla, dorsal agranular insula	mOccG, middle occipital gyrus			Left			
G, hypergranular insula			dlg, dorsal granular gyrus	IG			I	Left		
O	LOccC	lsOccG, lateral superior occipital gyrus	PPtha, posterior parietal Thal	Thal	S	Left				
		mOccG, middle occipital gyrus	PPtha, posterior parietal Thal			Left				
		msOccG, medial superior occipital gyrus	Stha, sensory Thal			Left				
	MvOccC	rCunG, rostral cuneus gyrus	NAC, nucleus accumbens	BG	S	Left				
P	IPL	A39c, caudal area 39PGp	dIPu, dorsolateral putamen			Left				
		A39c, caudal area 39PGp	Stha, sensory Thal	Thal	Left					
		A39c, caudal area 39PGp	PPtha, posterior parietal Thal		Left					
		A39rd, rostrrodorsal area 39 Hip3	PPtha, posterior parietal Thal		Left					
		A39rd, rostrrodorsal area 39 Hip3	Otha, occipital Thal		Left					
		A39rd, rostrrodorsal area 39 Hip3	cTtha, caudal temporal Thal		Left					
		A39rd, rostrrodorsal area 39 Hip3	IPFtha, lateral pre-frontal Thal		Left					
		A39rv, rostroventral area 39PGa	Stha, sensory Thal		Left					
		A39rv, rostroventral area 39PGa	PPtha, posterior parietal Thal		Left					
		A39rv, rostroventral area 39PGa	cTtha, caudal temporal Thal		Left					
		A40c, caudal area 40PFm	Stha, sensory Thal		Left					
		A40c, caudal area 40PFm	PPtha, posterior parietal Thal		Left					
		A40c, caudal area 40PFm	IPFtha, lateral pre-frontal Thal		Left					
		A40rd, rostrrodorsal area 40 PFT	Stha, sensory Thal		Left					
		A40rd, rostrrodorsal area 40 PFT	PPtha, posterior parietal Thal		Left					
		A40rd, rostrrodorsal area 40 PFT	cTtha, caudal temporal Thal		Left					

		A40rd, rostrrodorsal area 40 PFt	IPFtha, lateral pre-frontal Thal			Left
		A40rv, rostroventral area 40PFop	Stha, sensory Thal			Left
		A40rv, rostroventral area 40PFop	PPtha, posterior parietal Thal			Left
PocG		A1/2/3ulhf, area 1/2/3upper limb, head and face region	IPFtha, lateral pre-frontal Thal			Left
Prec		dmPOS, dorsomedial parietooccipital sulcusPER	PPtha, posterior parietal Thal			Left
SPL		A7pc, postcentral area 7	Stha, sensory Thal			Left
		A7c, caudal area 7	PPtha, posterior parietal Thal			Left
		A7pc, postcentral area 7	PPtha, posterior parietal Thal			Left
		A7ip, intraparietal area 7HIP3	PPtha, posterior parietal Thal			Left
T	STG	A22r, rostral area 22	A40rv, rostroventral area 40 PFop	IPL	P	Right
		A38l, lateral area 38	A39c, caudal area 39PGp			Right
		A38l, lateral area 38	A39rd, rostrrodorsal area 39 Hip3			Right
		A22r, rostral area 22	dmPOS, dorsomedial parietooccipital sulcus, PEr	Prec		Right
		A38l, lateral area 38	dmPOS, dorsomedial parietooccipital sulcus, PEr			Right
		TE1.0 & TE1.2	dmPOS, dorsomedial parietooccipital sulcusPER			Left
		A22r, rostral area 22	A7c, caudal area 7	SPL		Right
		A38l, lateral area 38	A7c, caudal area 7			Right
		A38l, lateral area 38	V5/MT+	LOccC	O	Right
		A38l, lateral area 38	lsOccG, lateral superior occipital gyrus			Right
		TE1.0 & TE1.2	msOccG, medial superior occipital gyrus			Left
		TE1.0 & TE1.2	lsOccG, lateral superior occipital gyrus			Left
		A22r, rostral area 22	rCunG, rostral cuneus gyrus	MvOccC		Right
		TE1.0 & TE1.2	vmPOS, ventromedial parietooccipital sulcus			Left
S	BG	dIPu, dorsolateral putamen	A7m, medial area7 PEp	Prec	P	Right
		NAC, nucleus accumbens	A7m, medial area7 PEp			
		NAC, nucleus accumbens	dmPOS, dorsomedial parietooccipital sulcusPER			
		NAC, nucleus accumbens	A31, area 31 Lc1			

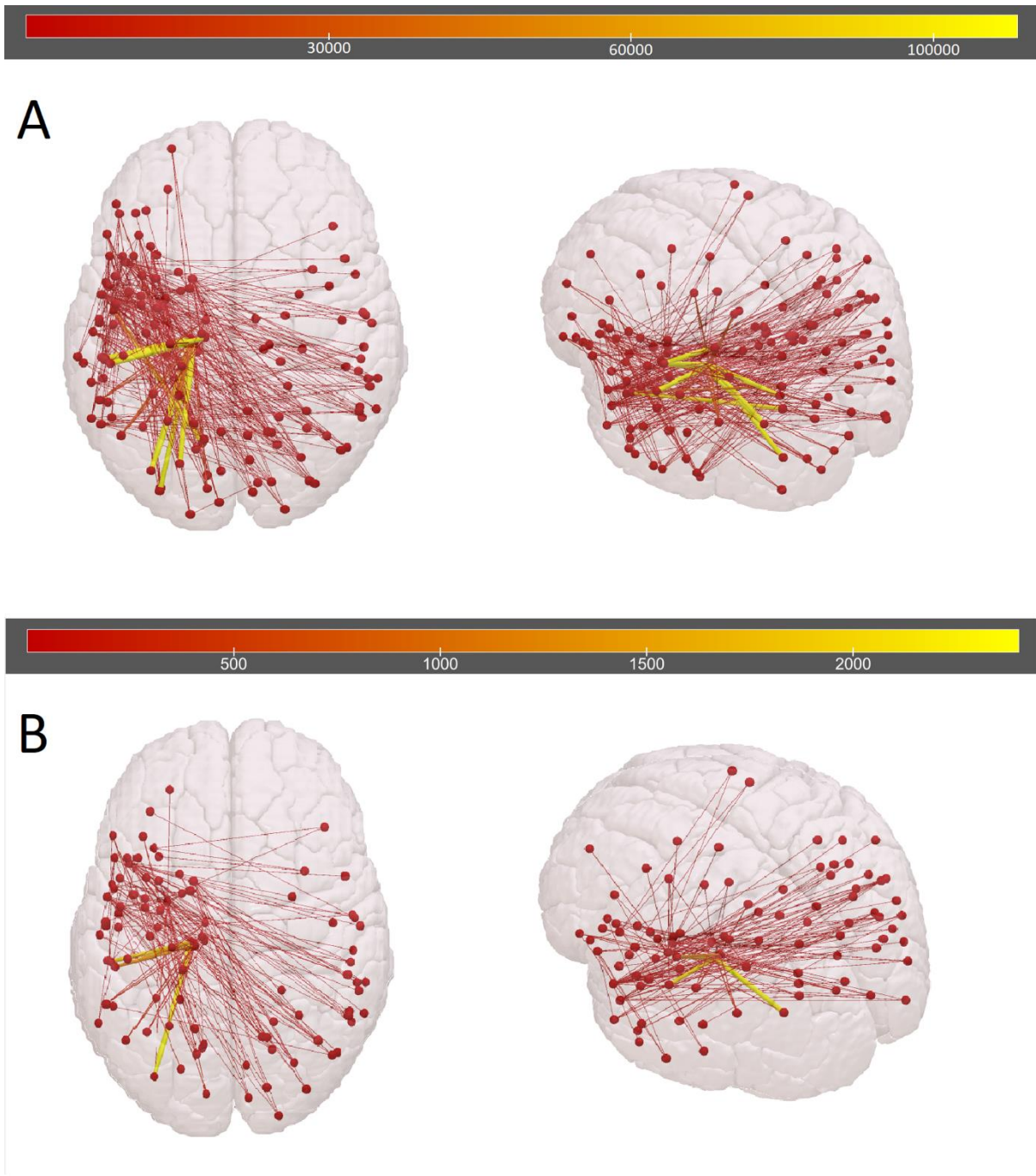
387 **Table 3 | Parcel-to-parcel disconnections significantly associated with a low multiplication**
388 **performance following the region-to-region disconnectivity analysis at $p < .05$ (corresponding to**
389 **Figure 3A). Each row denotes the side, lobe, gyrus and exact lable according to the BN-246 (Fan**
390 **et al., 2016) of each grey matter-to-grey matter disconnection. F = frontal, I = Insular, O =**
391 **Occipital, P = Parietal, T = Temporal, S = subcortical, IFG = Inferior Frontal Gyrus, MFG =**
392 **Middle Frontal Gyrus, PrcG = Precentral Gyrus, IG = Insular Gyrus, LOccC = Lateral Occipital**
393 **Cortex, MvOccC = Medioventral Occipital Cortex, IPL = Inferior Parietal Lobule, PocG =**
394 **Postcentral Gyrus, Prec = Precuneus, SPL = Superior Parietal Lobule, STG = Superior Temporal**
395 **Gyrus, BG = Basal Ganglia, Thal = Thalamus**

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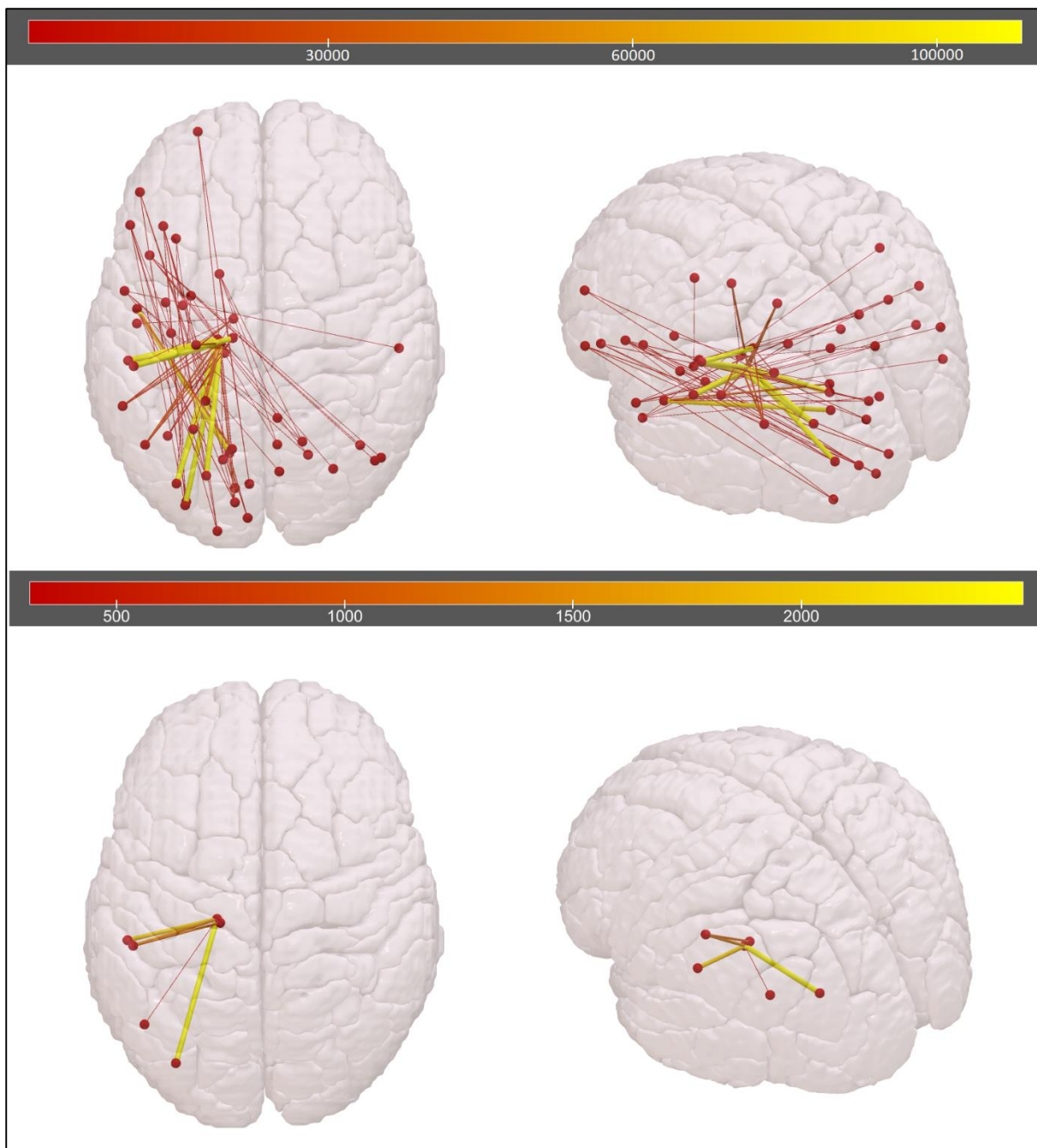
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401
402 **Figure 6 | Parcel-to-parcel disconnections following the Bayesian region-to-region**
403 **disconnectivity analysis.** The images presents the disconnections associated with a low
404 multiplication performance following BNHT with a $BF > 3$ (A) with all patients and (B) when
405 excluding the patient with zero points. Color scales reflect BF values whereby thicker and more
406 yellow edges denote higher BF.

407 Mapping multiplication score to ROI-to-ROI disconnectivity using Bayesian hypothesis testing
408 identified 313 connections with a $BF_{10} > 3$ suggesting evidence for H1, an effect of
409 disconnection on multiplication performance (see Figure 6, Panel A). Of the 7 disconnections
410 with the largest BFs ($BF_{10} > 10^5$), 6 were from the left thalamus to the left IPL, and one from
411 the left thalamus to the left middle occipital gyrus (yellow bars in Figure 6, Panel A). A table
412 including all values for all comparisons can be found in the supplementary material.

413



414

415 **Figure 7 | Parcel-to-parcel disconnections following the Bayesian region-to-region disconnectivity**
416 **analysis.** The images present the disconnections associated with a low multiplication performance
417 following BNHT with a $BF > 311$, making them comparable to those derived from the permutation-
418 based approach, as they are nearly equal to those that were significant in the frequentist analysis (A)
419 with all patients and (B) when excluding the patient with zero points. Color scales reflect BF values
420 whereby thicker and more yellow edges denote higher BF.

421

422 In Figure 7, Panel A, only disconnections with a $BF_{10} > 311$ are presented, to show that this
423 analysis is comparable to the permutation-based approach. These values suggest extreme
424 evidence for an effect (see Lee & Wagenmakers, 2013). This pattern looks identical to the
425 results provided by the GLM analysis. Again, hub-like structures were found for the left
426 thalamus, with 22 disconnections mainly to the left inferior and superior parietal lobules, 3 to
427 the left occipital gyrus, and 2 to the left precentral gyrus; the left IFG with 14 disconnections
428 to the left medioventral occipital cortex as well as the left lateral occipital cortex; and the left
429 STG, with 13 disconnections to the right inferior and superior parietal lobules (IPL, SPL), the
430 left and right precuneus, and right occipital areas. The disconnections with the strongest
431 evidence ($BF > 50,000$) were from the left parietal lobe to the thalamus, the left occipital lobe
432 to the thalamus, and one from the left occipital lobe to the left temporal lobe.

433 Similarly, when excluding the patient with 0 points, the same pattern of disconnections was
434 observed at a $BF_{10} > 311$ as in the permutation-based GLM (compare Figure 5B and 7B).

435 All in all, when comparing the results of the permutation-based analysis and the BNHT analysis
436 with or without the patient scoring zero points in the multiplication task, the most robust
437 disconnections appear to be those between the left IPL to the left thalamus.

438

439

440 4. Discussion

441 The present study evaluated how white matter disconnection affected arithmetic fact retrieval.
442 With the present patient sample it was not possible to examine the role of damage to grey
443 matter, as most lesions of our patients were within white matter (see lesion overlap, Figure 1),
444 providing insufficient power to analyse voxels within grey matter (see Kimberg et al.,2007).
445 We carried out four lesion-disconnection analyses in first-time stroke patients with unilateral
446 damage to either the left or right hemisphere performing a multiplication task. In the first
447 analysis, patients' lesions were superimposed on a white matter tractography map, leading to

448 individual disconnection topographies (Griffis et al., 2019). A whole-brain univariate analysis
449 suggested that disconnection of white matter fibers situated between the anterior AG and
450 posterior STS was associated with poorer multiplication performance. A second analysis was
451 carried out to investigate direct disconnections between two brain areas that could lead to low
452 multiplication performance. Single brain areas were defined as ROIs by a connectivity-based
453 grey matter atlas, and disconnection between each pair of regions was investigated for its role
454 in multiplication performance. We found several structures with multiple relevant
455 disconnections. These included the left thalamus, the left IFG, left and right (intra)parietal areas
456 such as the AG, STG, and left occipital areas. Single disconnections with the strongest
457 disconnection-deficit association were found between the left thalamus and the left IPS as well
458 as left occipital regions, but also between the left primary auditory cortex and left occipital
459 areas. As the patient with 0 points in the multiplication task affected some disconnections
460 disproportionately, we also replicated the previous analyses using Bayesian hypothesis testing
461 to quantify the evidence for the effect of disconnections on multiplication score, once with and
462 once without said patient. The most influential disconnections (i.e., those with the highest
463 Bayes Factors) when including all patients were almost identical to those in the previous
464 analysis using frequentist testing. Bayes Factors decreased when excluding the patient with 0
465 points, but the disconnection pattern was almost the same. The strongest disconnections were
466 from the left IPL to the left thalamus, followed by disconnections of the left IFG to left occipital
467 areas, again followed by several disconnections of the left STG and MTG to the right IPL. The
468 results of these analyses will be discussed in turn in the following.

469 Whole-Brain Analysis: Disconnection of the left AG with temporal areas

470 The findings of the whole-brain analysis fit well with a connectivity model of arithmetic fact
471 retrieval put forward by Klein et al. (2016). In this model, connections between the left MTG
472 and the left AG were considered necessary for arithmetic fact retrieval, as both areas are
473 essential elements of a left-hemispheric arithmetic fact retrieval network. A significant role of
474 the left AG for arithmetic fact retrieval has also been suggested by several neuropsychological
475 single case studies on arithmetic fact retrieval (e.g., Hittmair-Delazer et al., 1994; Lee, 2000;
476 Cohen et al., 2000). However, other single case studies have questioned the importance of the
477 AG within this network, as they reported patients presenting with a multiplication deficit
478 despite having a preserved AG (Cohen et al., 2000; Dehaene & Cohen, 1997; van Harskamp et
479 al., 2005; Zaunmueller et al., 2009). For example, patient ATH had severe difficulties verbally
480 solving multiplication problems while making only a few mistakes in subtraction (Cohen et al.,

481 2000). On the other hand, Van Harskamp & Cipolotti (2001) reported on a patient who did not
482 show a multiplication deficit, although damage to left parietal regions, including the AG,
483 occurred.

484 Given both the current results and more recent research, inconsistent results of single case
485 studies can be explained by the approach of Klein and colleagues (2016): The disconnection
486 cluster indicated by our analysis to be associated with arithmetic fact retrieval involved the left
487 arcuate fasciculus, the temporopontine tract and U-fibers between the AG and STS. This
488 observation suggests that disconnection of the AG with temporal areas, such as STS, STG, and
489 MTG seems to cause an arithmetic fact retrieval deficit. This expands the results of previous
490 studies indicating the detrimental effect of lesions to or disconnection of the AG. In this sense,
491 Klein et al. (2013b) re-evaluated a single case reported by Zaunmueller et al. (2009), focusing
492 on lesions to the patient's white matter compared to previous single case studies focusing on
493 lesions more on grey matter damage. While the lesion itself was in the basal ganglia, it also
494 incorporated white matter fibers that explicitly connect frontal areas with the AG, suggesting
495 that the patient could not retrieve arithmetic facts due to poor connectivity of the AG. Similarly,
496 Mihulowicz et al. (2014) conducted a voxel-based lesion behavior mapping study observing
497 that white matter lesions to superior parts of the superior lateral fasciculus (SLF II) impaired
498 arithmetic fact retrieval.

499 The current findings provide the first evidence of indirect measures of disconnection on
500 arithmetic fact retrieval on the group level, further corroborating the role of the left AG within
501 the arithmetic fact retrieval network. They can explain case studies questioning the role of the
502 left AG in multiplication, whereby patients with multiplication deficits without damage to the
503 AG or other grey matter areas of the network may have suffered from structural white matter
504 disconnectivity within the network, as suggested by Klein et al. (2013b, c).

505 Importantly, neurofunctional evidence from healthy participants on learning complex
506 multiplication facts (e.g., Delazer et al., 2003, 2005; Ischebeck et al., 2006, 2007; Grabner et
507 al., 2009; Rickard et al., 2000; Zamarian et al., 2009) also indicates that the left AG plays a
508 crucial role in arithmetic fact retrieval. Bloechle et al. (2016) evaluated fMRI signal before and
509 after multiplication training. They found a stronger fMRI signal in the left AG when comparing
510 trained vs. untrained multiplication tasks after training only, but no difference in activation
511 when directly comparing the same multiplication problems across training (post- vs. pre-
512 training). Therefore, the authors suggested that the left AG might act as a 'circuit breaker',

513 coordinating whether a task is to be solved purely via fact retrieval or whether a switch in
514 strategy requiring additional cognitive processing, such as calculation, is necessary.

515 This aspect provides a compelling explanation for patient FS's ability to multiply correctly
516 despite damage to parietal areas, including the left AG: They were still able to recall
517 multiplication facts due to an intact temporal retrieval network and did not require the left AG
518 to switch from fact retrieval to calculation. In the current study, most patients with an arithmetic
519 fact retrieval deficit also suffered from aphasia. Accordingly, they might not have been able to
520 recall phonologically stored arithmetic facts initially. When attempting to switch to a
521 calculation-based strategy, these patients were also slowed due to the disconnection of left AG.
522 Therefore, a possible explanation for the given findings may be that when arithmetic fact
523 retrieval fails, the AG is involved in switching the strategy by which a task is solved. When it
524 is disconnected or damaged, this switch fails.

525 Region-to-Region Disconnectivity

526 Results of the region-to-region disconnectivity analyses indicate several disconnections
527 between left-hemispheric areas, as well as from left temporal areas to right parietal areas, being
528 associated with deficits in arithmetic fact retrieval. Several disconnection groupings were
529 significant (Fig. 3). First off, all analyses found the most disconnections of the left thalamus
530 with parietal areas (see also Fig. 7), meaning that these results were robust over both the
531 permutation approach as well as BNHT, with and without the patient with zero points in the
532 task. This suggests that a disconnection of the left thalamus with left parietal areas was most
533 likely to lead to a low multiplication performance in the current sample. This fits with previous
534 evidence that both areas are involved in arithmetic fact retrieval (e.g., Arsalidou & Taylor,
535 2011). In particular, the thalamus is generally involved in various cognitive processes, such as
536 memory, language or mental set-shifting (see Saalman & Kastner, 2015 for an overview).
537 Therefore, it seems sensible that it also is involved in mental arithmetic (Arsalidou & Taylor,
538 2011; Johnson & Ojemann, 2000; Koyama et al., 2020). On the other hand, the IPS is known
539 to be involved specifically in magnitude processing (for meta-analyses, see Arsalidou &
540 Taylor, 2011; Arsalidou et al., 2018; Dehaene et al., 2003; Hawes et al., 2019).. Yet, arithmetic
541 tasks are typically not solved exclusively by either arithmetic fact retrieval or magnitude
542 manipulations (i.e., calculations). Instead, they are solved by an adaptive interplay between
543 both (Klein et al., 2016). It thus seems possible that arithmetic fact retrieval deficits following
544 disconnection between the thalamus and the IPS reflect difficulties in switching between and

545 integrating fact retrieval and magnitude manipulation strategies, as already argued on the
546 whole-brain level. In conclusion, the thalamus may be considered as a sort of central relay of
547 information between different cortical areas, receiving, coordinating, and transmitting
548 information across the cortex. Therefore, it should not be surprising that disconnection of such
549 a vital structure with areas associated with number processing, such as left-hemispheric parietal
550 areas, would lead to deficits in multiplication.

551 Our results also showed several disconnections of the left IFG with left (parieto-)occipital
552 areas. While previous research reported essential connections between parietal regions, such
553 as the AG, and the IFG (e.g., Klein et al., 2016), the role of fronto-occipital connections in
554 arithmetic has not been focused on so far. However, it is known that the IFG is connected with
555 the parietal and occipital cortex via the inferior fronto-occipital fasciculus (IFOF). This
556 suggests that disconnection of certain parts of the IFOF may also lead to arithmetic fact
557 retrieval deficits. The EC/EmC system corresponds to a rostral/anterior segment of the IFOF
558 (Willmes et al., 2014) and is considered as part of a ventral pathway involved in arithmetic fact
559 retrieval (Klein et al., 2016). More precisely, Klein et al. (2013b) found that arithmetic tasks
560 that can be solved via arithmetic fact retrieval were associated with a ventral processing route.
561 This route ranges from frontal regions, such as the medial frontal gyrus, to parietal regions,
562 including the AG via the middle longitudinal fascicle (MdLF), which itself is part of the
563 EC/EmC system. They suggested that this connection serves the purpose of phonological or
564 semantic access, similar to language processes (e.g., Saur et al., 2008; Weiller et al., 2011).
565 Therefore, in the current study, the observed disconnections might have led to language-related
566 errors, such as semantic or phonemic paraphasias.

567 Finally, we observed several disconnections of the left STG associated with an arithmetic fact
568 retrieval deficit. Most of these disconnections were to areas around the IPS bilaterally.
569 Disconnections of the left STG to left IPS fit well with a series of fMRI studies in healthy
570 adults (Prado et al., 2011) as well as children with and without mathematical learning
571 disabilities (e.g., Berteletti et al., 2011; Demir et al., 2014) that suggest that the STG, as well
572 as the MTG, play a role in arithmetic fact retrieval. Regarding the results on disconnections to
573 the right IPS, it has been shown several times by Semenza and colleagues that the right parietal
574 cortex is crucially involved in multiplication tasks: For example, Semenza et al. (2017) applied
575 direct cortical stimulation to patients during tumor resection. These were carrying out a
576 multiplication task while having either their left or their right parietal cortex stimulated. When
577 the right parietal cortex was stimulated, patients tended to make more retrieval-based errors

578 (i.e., deriving wrong solutions within multiplication tables) compared to approximation errors
579 (a number numerically close to the correct solution). In contrast, when their left parietal cortex
580 was stimulated, this proportion changed to about half retrieval-based, and half approximation-
581 based errors. In two further studies examining multiplication with MEG (Arcara et al., 2021;
582 Salillas et al., 2021), the role of right parietal and frontal areas was substantiated, adding to
583 existing evidence. This suggests that the right parietal cortex plays an important role in
584 examining the ‘plausibility’ of a solution generated by the left hemisphere by estimating the
585 approximate magnitude of the solution. Therefore, it is possible that in case a patient retrieved
586 a wrong solution, the disconnection of right parietal areas may have impaired this estimation
587 of approximate magnitude and thus a reappraisal of the initially retrieved response.

588

589 The bilateral arithmetic fact retrieval network

590 Taken together, the current results indicate that arithmetic fact retrieval in multiplication is
591 subserved by a widely connected network including the left-hemisphere areas suggested by
592 Klein et al. (2016) as well as areas around the right IPS. The whole-brain analyses corroborated
593 the idea that the left angular gyrus plays a central role in arithmetic fact retrieval (e.g., Delazer
594 et al., 2003; Dehaene et al., 2003) as disconnected voxels ranging from the AG to left temporal
595 areas led to impaired arithmetic fact retrieval. However, the region-to-region analyses revealed
596 that not only left AG connectivity but also connectivity of the left and right parietal lobes, as
597 well as further left-hemispheric areas, such as the thalamus, seems to be necessary for the
598 successful retrieval of arithmetic facts. As regards the role of the AG in the fact retrieval
599 network, we suggest that the left AG may not be the (sole) storage location of arithmetic facts.
600 Instead, it may serve a more regulatory role within the network, for instance, subserving
601 semantic integration of concepts (Amalric & Dehaene, 2017; Price et al., 2015) or strategy
602 switching (Bloechle et al., 2016). For instance, patients who could not solve tasks via arithmetic
603 fact retrieval may have had to switch to a different strategy requiring increased magnitude
604 processing (e.g., Dehaene et al., 2003; Klein et al., 2016). If these processing routes to the IPS
605 of either hemisphere were also disconnected (i.e., due to a lesion affecting both association and
606 commissural fibers), patients might not have been able to use this compensatory mechanism
607 adequately. Consequentially, they committed errors or took longer than the ten-second cut-off
608 time to solve the task.

609 It has been argued that, even within multiplication tasks, there is a size effect, leading to a
610 difference between tasks with multipliers over 5 and those with multipliers under 5 (see
611 Zbrodoff & Logan, 2005). Similarly, Salillas et al. (2012) suggest that in difficult tasks only,
612 TMS disruption of the vertical IPS bilaterally could increase reaction times in a multiplication
613 task. Yet, as we used a standardised subscale from the well-established NPC battery (Delazer
614 et al., 2003), which is based on accuracy measures on a strictly limited number of items (i.e.,
615 36 for arithmetic fact retrieval), effects of problem size in multiplication cannot be evaluated
616 in the current data. Therefore, future work would be desirable to explicitly address the potential
617 effects of problem size in arithmetic fact retrieval with tools better balanced for stimulus
618 magnitude and difficulty.

619 Conclusion

620 Our data on lesion-disconnection analyses in unilateral stroke patients suggest that a deficit in
621 arithmetic fact retrieval cannot be tracked to a single locus within the brain. Instead,
622 impairments in arithmetic fact retrieval seem to originate from disconnections of several areas
623 within a (mostly) left-hemispheric network around parietal areas such as the AG, thalamus,
624 STS, STG, MTG and IFG. Interestingly, in both addition and subtraction, patients'
625 performance was very close to ceiling level, indicating that these disconnections may be
626 detrimental specifically to multiplication fact retrieval. Yet, it has to be noted that this is only
627 an indirect inference as it was not possible to analyse associations of disconnections and
628 addition/subtraction performance explicitly due to the lack of variance in the performance data.
629 Therefore, future research would be desirable to test these tasks more specifically. On a more
630 general level, our study underlines the relevance of future research, taking into account grey
631 matter integrity and white matter connectivity in numerical cognition and cognition in general.

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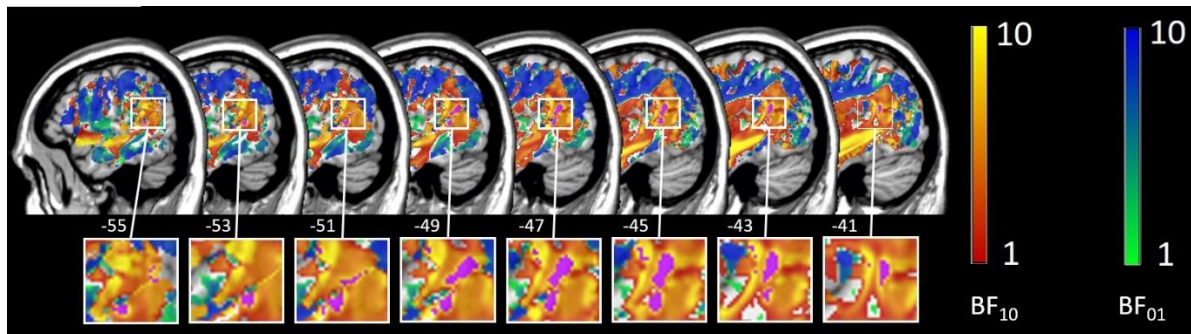
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896

897 Appendix

898

899 Appendix A:



900

901 **FIGURE 4 | Bayesian disconnectivity mapping after exclusion.** Sagittal View of the left hemisphere.
902 The heatmap denotes Bayes factors of correlations between voxel-wise disconnection value and
903 multiplication score. Voxels marked in a red-to-yellow manner had BFs indicating evidence for their
904 association with multiplication score, while voxels marked in green-to-blue indicate evidence for no
905 association with multiplication score. Purple indicates the voxels that were significant following the
906 frequentist analysis (see Figure 2). The sagittal x-coordinate of standardized MNI space is given below
907 each slice. Note that in this image the scale starts at 1, as no logarithms are displayed.

908

909

910 Competing interests

911 The authors have no competing interests to disclose.

912

913 Acknowledgements

914 This work was supported by the Deutsche Forschungsgemeinschaft (KL 2788/2-1 und KA
915 1258/24-1). We thank all patients who participated in this study as well as the nursing staff of
916 the University of Tuebingen who assisted with patient preparation.

Online materials, including all analysis scripts, descriptive data, and resulting topographies, are publicly available at <http://dx.doi.org/10.17632/yjkr647mzb.1>. The clinical datasets analyzed in the current study are not publicly available due to the data protection agreement approved by the local ethics committee and signed by the participants.