Left angular gyrus disconnection impairs multiplication fact retrieval

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Abstract

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

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

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

Keywords

1. Introduction

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

The retrieval of rote learned arithmetic facts has been assumed to be processed multi-modularly and distributed within a left-lateralized language network, including inferior frontal gyrus (IFG; Delazer et al., 2003), middle and superior temporal gyri (MTG/STG), supramarginal gyrus (SMG), angular gyrus (AG; e.g., Dehaene et al., 2003; Delazer et al., 2003; Grabner et al., 2009a; 2009b), and hippocampus (e.g., Bloechle et al., 2016; Klein et al., 2016; 2019). However, the exact role of some of these areas is still debated. On the one hand, several case studies reported patients with a preserved AG who presented selective deficits for arithmetic fact retrieval (as measured by a multiplication task, Cohen et al., 2000; Dehaene & Cohen, 1997; Van Harskamp et al., 2005). Moreover, the role of the hippocampus, which is assumed a key structure for long-term memory in general, is not yet fully understood.

Delazer and colleagues (2019), for instance, suggested that the hippocampus plays a crucial role in encoding and consolidating arithmetic facts, but not in their actual retrieval after consolidation in memory. On the other hand, it has been criticized that the interaction of several of these areas, which are activated during arithmetic fact retrieval, may not be specific to arithmetic fact retrieval. For instance, IFG, STG, and SMG are typically also involved in phonological decoding during language processing (Prado et al., 2011; Vigneau et al., 2006; for a review, see Price, 2012). Similarly, modulation of AG (de)activation, observed for arithmetic fact retrieval, was also found for non-mathematical content (Ischebeck et al., 2007;

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74 Zamarian et al., 2009). Therefore, it appears likely that (sub)processes of arithmetic fact
75 retrieval are related to language processing.

76 However, such an association between arithmetic fact retrieval and language processing is still
77 debated. Amalric and Dehaene (2016, 2017, 2019) suggested that simple, overlearned
78 arithmetic facts might be processed independently of left-hemispheric language areas. 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 Klein et al. (2016) provided first evidence for white matter connectivity underlying arithmetic
87 fact retrieval using probabilistic fiber tracking in healthy participants. The authors showed that
88 parietal areas are connected with frontal areas dorsally via the cingulate bundle and ventrally
89 via the extreme/external capsule system and temporal areas via the inferior longitudinal
90 fascicle. The importance of the integrity of such a network architecture for fact retrieval has
91 already been highlighted in some studies: For instance, in a re-evaluation of a single case
92 reported by Zaunmueller et al. (2009), Klein et al. (2013b) found that the lesion was limited to
93 the basal ganglia region (and did not involve the AG) but nevertheless led to disruption of white
94 matter fibers connecting frontal areas with the AG. Based on this, the authors suggested that
95 the patient could not retrieve arithmetic facts because of a disconnection within their retrieval
96 network and not because of actual grey matter damage in cortex areas associated with fact
97 retrieval. In this vein, Mihulowicz et al. (2014) conducted a voxel-based lesion behaviour
98 mapping study (VLBM). They observed a significant association of lesions in the dorsal
99 pathway (i.e., parts of the superior lateral fasciculus) with arithmetic fact retrieval.

100 Only recently, lesion-disconnectome mapping has brought forward the possibility to more
101 closely examine the role of network disruption of brain lesions in post-stroke cognitive deficits.
102 In particular, it allows for an indirect assessment of lesion-induced disconnections by reference
103 to healthy connectome data (e.g., Griffis et al., 2019). In the current study, we evaluated brain
104 disconnections associated with a deficit in arithmetic fact retrieval in acute left- and right-
105 hemisphere stroke patients at the group level. We expected that white matter disconnections

106 within the left-hemispheric arithmetic fact retrieval network, including, among others, AG,

107 MTG, and hippocampus, should be associated with deficits in arithmetic fact retrieval. In a

108 subsequent analysis, we further aimed at evaluating which disconnections between two specific

109 grey matter regions are significantly associated with a deficit in arithmetic fact retrieval.

110

2. Methods

112 2.1 Participants

113 We used the existing patient data set from Mihulowicz et al. (2014) and added 28 new patients

114 for the present analyses. In total, 73 native German-speaking acute stroke patients participated

115 in the study. All of them were patients consecutively admitted to the Center of Neurology at

116 Tübingen University Hospital over 33 months (cf. Mihulowicz et al., 2014) plus another 18

117 months. Among these, 38 patients presented left hemisphere damage (LHD) and 35 patients

118 right hemisphere damage (RHD). Patients were only included when they presented an MR- or

119 CT-documented cerebral stroke, not more than 14 days post-stroke. We did not include patients

120 with previous lesions, other neurological or psychiatric diseases, substantial micro-angiopathy

121 or white matter alterations. Patients or their relatives gave their informed consent to participate

122 in the study. The study followed the ethical standards in the Declaration of Helsinki (Version

123 2013) and was approved by the local ethics committee (Vote 82/2018 BO2). Clinical and

124 demographic data for the whole group of 73 patients are given in Table 1; an illustration of

125 lesion overlap of all participants can be seen in Figure 1.

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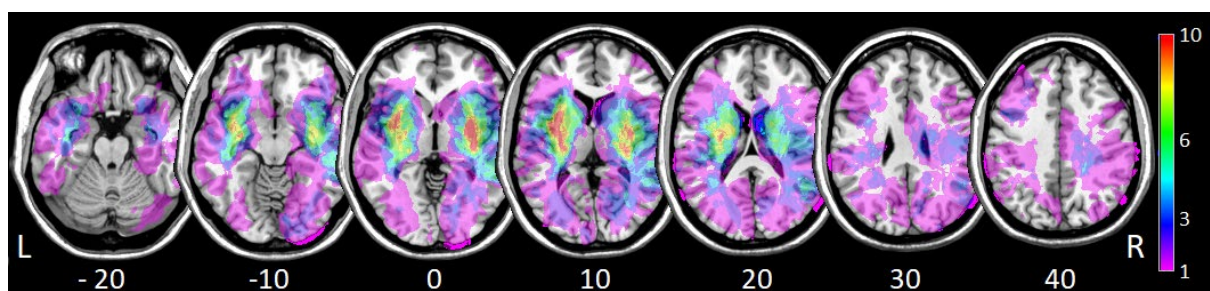127 --- Table 1 and Figure 1 near here ---

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130 **FIGURE 1| Lesion Overlap.** Overlap of all lesions included in the analysis. The color bar indicates
131 the frequency of lesion overlap. The vertical z coordinate of standardized MNI space is given below
132 each slice.

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

		LHD	RHD
N		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

135

136   2.2 Procedure

137   Patients were investigated in sitting position. The entire experiment took about one hour and
138   was completed in one session for most patients. For some, further sessions were needed due to
139   clinical examinations or because they needed a break. For the multiplication task, patients
140   responded verbally and in written form when the former was not possible.

141   We ensured that all patients were able to follow the task instructions. In particular, we tested
142   receptive and expressive language abilities in LHD patients. For *language comprehension*, we
143   used the 'Colour-Figure` subtest from the German adaptation of the Aphasia Check List (ACL;
144   Kalbe et al., 2005). For *language production*, we applied the 'Picture naming task' of the
145   Aachener Aphasia-Bedside Test (AABT; Biniek et al., 1992).

146   We also tested patients with RHD for *spatial neglect*. The neglect test comprised the 'Letter
147   Cancellation Task' (Weintraub & Mesulam, 1985), the 'Bells test' (Gauthier et al., 1989), as
148   well as a copying task (Johannsen & Karnath, 2004). Patients were diagnosed with spatial

149   neglect if they scored above the respective cut off as per manual in at least 2 out of 3 tests. We

150   calculated the Centre of Cancellation (CoC) for the two cancellation tasks, using the procedure

151   and cut-off scores for diagnosing spatial neglect described by Rorden and Karnath (2010).

152   In the copying task, patients were asked to copy a complex multi-object scene consisting of

153   four figures (a fence, a car, a house, and a tree), with two of them located in each half of the

154   horizontally oriented sheet of paper. Omission of at least one of the contralateral features of

155   each figure was scored as 1. The omission of each whole figure was scored as 2. One additional

156   point was given when contralaterally located figures were drawn on the ipsilesional side of the

157   paper sheet. The maximum score was 8. A score higher than 1 (i.e. > 12.5% omissions) was

158   taken to indicate neglect.

159   Visual field deficits were assessed in all patients via the standard confrontational procedure.

160   Table 1 presents all clinical data.

161

162   2.3 Stimuli

163   As part of our battery, we evaluated patients' arithmetic fact retrieval through a single-digit

164   multiplication production task (i.e., 42 items from arithmetical tables up to 9×9), included in

165   the standardized neuropsychological Number Processing and Calculation Battery (NPC;

166   Delazer et al., 2003). Each multiplication problem was presented on a separate A4 sheet (black

167   digits printed on white paper, digit height: 7 mm). Sheets were aligned centrally on a table in

168   front of the patient. To operationally determine impaired performance, we used the cut-off

169   criteria provided for the NPC (cf. Delazer et al., 2003). According to the standardized NPC

170   procedure, testing was stopped after five consecutive incorrect or missing responses, and no

171   time limit was imposed. However, responses lasting longer than 10 seconds were rated as

172   incorrect, as this implies a failure in instant fact retrieval. Self-corrections were allowed.

173   One aphasic LHD patient could not solve the single-digit multiplication production task orally

174   or in writing, while he could solve 24 of 25 addition tasks correctly in verbal form. In this

175   patient, we applied a multiple-choice version of the multiplication task also provided in the

176   NPC to determine a core deficit in multiplication processing rather than a language difficulty.

177   The multiple-choice version tested the same multiplication problems (e.g., 6 x 7) by providing

178   four solution probes (i.e. correct solution, 42; one operand error, e.g., 45, one table error, e.g.,

179 49, and one close-miss error, e.g., 39). The patient showed deficits in the multiple-choice

180 version. Accordingly, he was included in data analysis.

181

182 2.4 Lesion Analysis

183 We used diffusion-weighted MRI images taken within 48h after stroke (Weber et al., 2000) or

184 else T2-weighted fluid-attenuated inverse-recovery (FLAIR) images (Brant-Zawadzki et al.,

185 1996; Noguchi et al., 1997; Ricci et al., 1999; Schaefer et al., 2002). In case MR imaging was

186 not conducted, CT images were used (MRI: N=29; CT: N=44). When several imaging data sets

187 existed for an individual patient, we used the session closest in time to behavioral testing

188 showing a clear demarcation. Lesion borders were marked semi-automatically using the

189 'Clusterize Toolbox' (de Haan et al., 2015). Then, both the anatomical scan and the lesion map

190 were normalized into stereotaxic space using the 'Clinical Toolbox' (Rorden et al., 2012;

191 www.mccauslandcenter.sc.edu/CRNL/clinical-toolbox) implemented in SPM12

192 (www.fil.ion.ucl.ac.uk/spm).

193

194 2.5 Whole-brain disconnectivity mapping

195 We created individual white matter disconnectivity topographies for each patient. These

196 topographies indicate the proportion of disconnected fibers for each white matter voxel in the

197 brain imaging space running through this voxel. Thereby, it allows a topographical assessment

198 of a lesion's impact on brain connectivity as a whole. To this end, we applied the Lesion

199 Quantification Toolkit (LQT; Griffis et al., 2021). The LQT utilizes a tract-wise connectome

200 atlas and embeds the patient's lesion map into it. The toolkit identifies all fiber streamlines that

201 intersect with the lesion and maps connectome-wide disconnection induced by the lesion. We

202 used the LQT's standard HCP-842 atlas (Yeh et al., 2018) for atlas-based tractography, keeping

203 the default parameter setting as suggested in the LQT manual.

204 Subsequently, we further analyzed these continuous disconnectivity maps using mass-

205 univariate General Linear Models in 'NiiStat' (https://github.com/neurolabusc/NiiStat). Only

206 voxels with a disconnection in at least five patients were considered in the analysis. Tests were

207 performed one-sided at p<0.05 and corrected for family-wise errors. The family-wise error rate

208 was corrected using 5000 permutations with maximum statistic permutation (Nichols &

209 Holmes, 2002). This disconnectivity topography mapping thus identified voxels for which

210 disconnection is associated with a more severe deficit in multiplication.

211

212 2.6 Region-to-region disconnectivity

213 We additionally analyzed parcel-wise disconnectivity as provided by the LQT. This procedure

214 allowed us to identify which direct disconnections between two grey matter regions are

215 significantly associated with a deficit in the multiplication task. We created a structural

216 connectivity matrix by combining the provided tractography atlas and the Brainnetome Atlas

217 (BN-246, Fan et al., 2016) as our parcellation atlas. The BN-246 is multi-modally derived,

218 contains 210 cortical and 36 subcortical subregions and was developed specifically for

219 connectivity analyses. The number of streamlines disconnected by the lesion map between each

220 pair of parcels was converted to a percentage of disconnected streamlines, resulting in

221 symmetric 246-by-246 disconnectivity matrices. We subjected these matrices to a mass-

222 univariate analysis to identify associations between disconnection and the deficit using custom

223 scripting in MATLAB R2020a. Following the strategy of the topographical analysis of brain-

224 wide disconnectivity maps described above, we employed mass-univariate general linear

225 models with a family-wise error correction by maximum statistic permutation (Nichols &

226 Holmes, 2002).

227 We loaded disconnection matrices into MATLAB and removed the diagonal and redundant

228 elements below it. Many ROI-to-ROI disconnections were rarely or never present in the data,

229 likely either because the sample's lesion anatomy did not include damage to the connection or

230 because the connection was physiologically non-existent. Therefore, we identified the sum of

231 all patients with a disconnection present (i.e., a disconnection score > 0) for each ROI-to-ROI

232 connection. We removed all connections affected in less than 15 patients from the analysis,

233 reducing the final set of analyzed connections to 955. We then computed a general linear model

234 for each ROI-to-ROI connection with the independent variable disconnectivity score and the

235 dependent variable multiplication performance. Then, maximum statistic permutation with

236 50.000 permutations was employed on permuted behavioral data and the original disconnection

237 data with the same analysis strategy to assess the distribution of maximum statistics under the

238 null hypothesis. We obtained a one-sided, corrected threshold for statistical significance at $p <$

239 0.05 by identifying the 95th percentile of permutation-derived maximum statistics. To identify

240 those connections most strongly associated with the deficit, we then identified a smaller set of

241 the strongest disconnection-deficit associations at $p < 0.01$.

242

243 2.7 Data availability

244 Online materials, including all analysis scripts, descriptive data, and resulting topographies, are

245 publicly available at http://dx.doi.org/10.17632/yjkr647mzb.1. The clinical datasets analyzed in

246 the current study are not publicly available due to the data protection agreement approved by

247 the local ethics committee and signed by the participants.

248

3. Results

250 3.1 Behavioral measures

251 Table 2 summarizes the behavioral results of the multiplication task. Items involving '0' or '1

252 as operands (n=6) were excluded from the analysis because they address rule-based processing

253 (McCloskey et al., 1991). While the analysis used continuous values, five patients in the RHD

254 group performed below the typical cut-off in the multiplication task; in the LHD group, ten

255 patients did so, including one aphasic patient who could not respond to the multiplication task

256 orally or in writing. They were presented with a multiple-choice version (see above).

257 --- Table 2 near here ---

258

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

259

260 3.2 Brain-wide disconnectivity mapping

261 Figure 2 (Panel A) illustrates the average percentage of lesion-induced disconnection for all 73

262 patients. Deficits in single-digit multiplication were significantly associated with the

263 disconnection of a single cluster around x = (-59; -40), y = (-57; -39), and z = (3; 22), affecting

264 areas defined by the HCP-842 as the left arcuate fasciculus, temporopontine tract, and U-fibers

265 between the AG and superior temporal areas (see Figure2 (Panel B).

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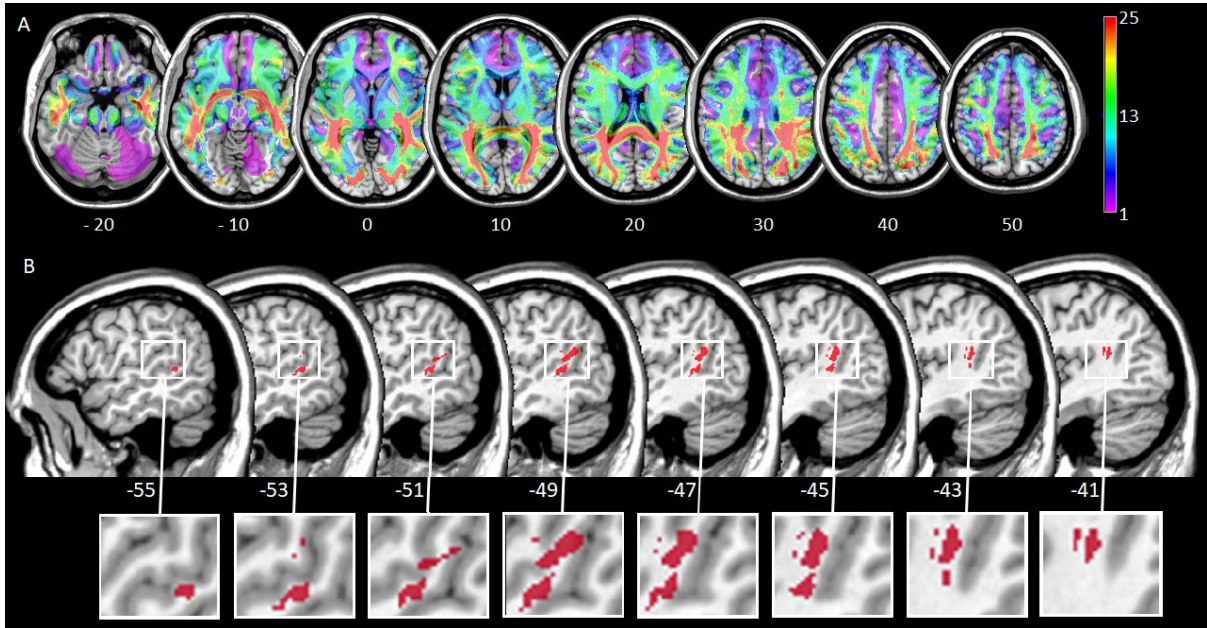267 --- Figure 2 near here ---

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269
270 **FIGURE 2 | Disconnectivity mapping.** (A) The percentage of fibre disconnection as indicated by the
271 average reduction in streamline density is color-coded from 1 (pink) to 25 (red), whereby the maximum
272 value in a patient was 36. A higher number indicates a higher percentage of fibre disconnection.
273 Topographies can be viewed in the online data. The vertical z coordinate of standardized MNI space is
274 given below each slice. (B) Sagittal view of the left hemisphere. Statistical voxel-wise lesion-behavior
275 mapping (VLBM) analyses using mass-univariate general linear models in multiplication. Plotted are
276 voxels that survived permutation-test based FWE correction at $p < 0.05$ (left hemisphere). The sagittal
277 x coordinate of standardized MNI space is given below each slice.

278

279 3.3 Region-to-region disconnectivity

280 Mapping multiplication score to ROI-to-ROI disconnectivity using general linear models

281 identified 36 connections significant at $p < 0.05$ (see Figure 3 (Panel A), Table 3). The

282 disconnectome revealed several regions that stood out due to several disconnections associated

283 with the multiplication deficit. A hub-like structure was found for the left thalamus, with 17

284 disconnections mainly to the left inferior and superior parietal lobules, including PGa of the

285 angular gyrus. Furthermore, 6 disconnections between the left IFG and the medioventral

286 occipital cortex as well as the left lateral occipital cortex were also associated significantly with

287 poorer multiplication scores. Finally, further 5 disconnections from the left STG to the right

288 inferior and superior parietal lobules (IPL, SPL), as well as to the right precuneus, were

289 significant.

290 To facilitate the interpretation of the strongest predictors, we then set the threshold to $p < 0.01$.

291 This procedure revealed a small set of 3 left-hemispheric disconnections to have the strongest

292 association with poorer multiplication scores (see Fig. 3 (Panel B)): Te1.0 / Te1.2 of the

11

293   primary auditory cortex with the ventromedial parietooccipital sulcus, posterior parietal

294   thalamus with IPS (rostroventral area 40) and the left caudal temporal thalamus with the IPS

295   (rostrodorsal area 40).

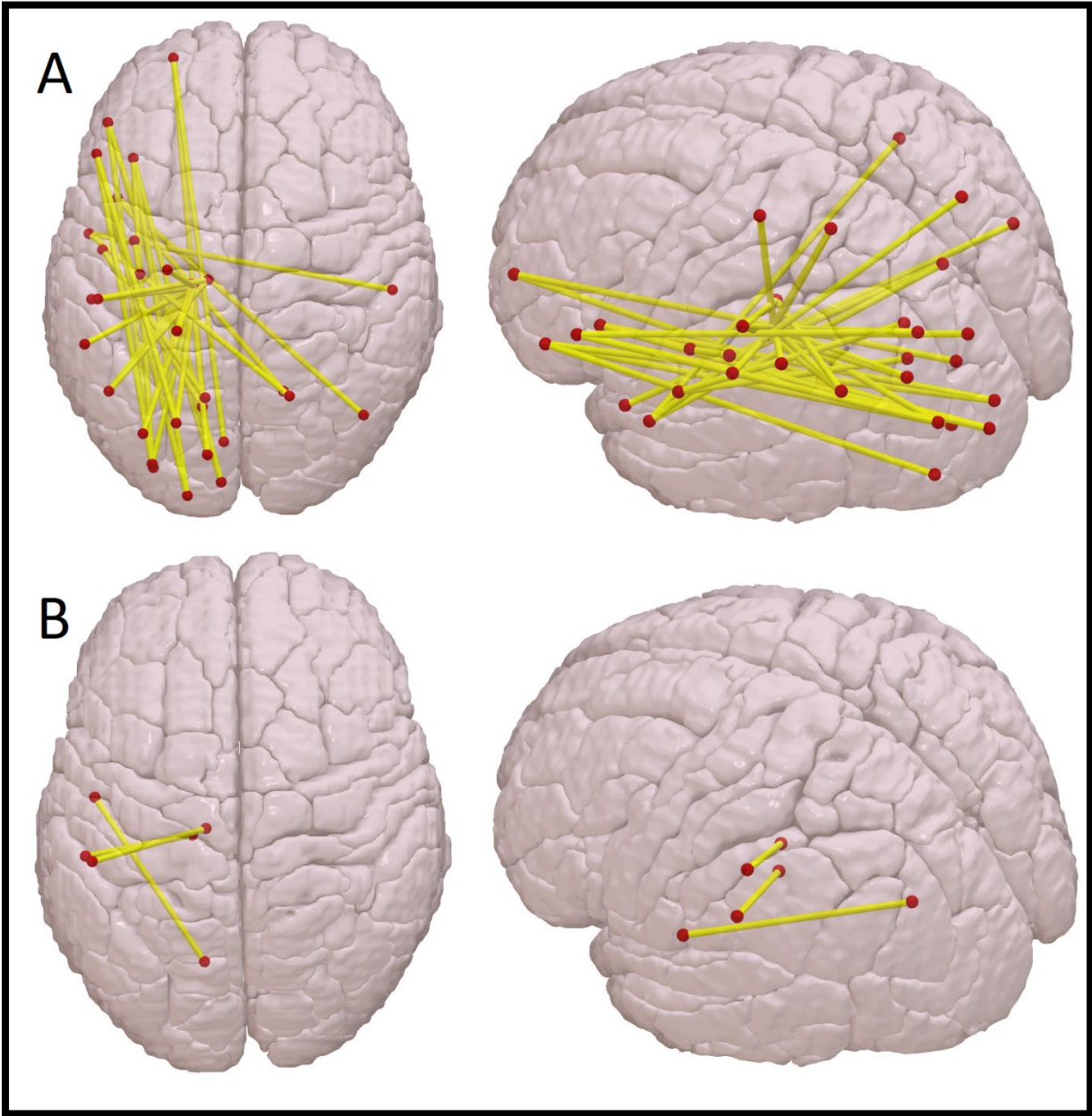296   --- Table 3 and Figure 3 near here ---

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298
299   **Figure 3 | Parcel-to-parcel disconnections following the region-to-region disconnectivity analysis.**
300   (A) presents the disconnections significant at $p < .05$, (B) those at $p < .01$.

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Side	Lobe	Gyrus	Label	Label	Gyrus	Lobe	Side
Left	Parietal	SPL	A7c, caudal area	A22r, rostral area	STG	Temporal	Left
			rostroventral area 40 (Pfop)	A22r, rostral area			
			dmPOS, dorsomedial parietooccipital sulcus	RIGHT TE1.0_and_TE1.2			Right
	Occipital	Medioventral occipital cortex	ventromedial parietooccipital sulcus	RIGHT TE1.0_and_TE1.2			
			caudal lingual gyrus	lateral area 10	MFG	Frontal	Left
				rostral area 45	Orbital Gyrus		
			rostral cuneus gyrus	lateral area 10	MFG		
			caudal cuneus gyrus	rostral area 45			
				opercular area 44	IFG		
		Lateral occipital cortex	lateral superior occipital gyrus	caudal area 45			
			middle occipital gyrus	caudal area 45			
				opercular area 44			
			occipital polar cortex	caudal area 45			
				opercular area 44			
			inferior occipital gyrus	rostral area 45	Orbital Gyrus		
	Subcortical	Thalamus	sensory thalamus	postcentral area 7	SPL		
				1rostral area 45	Orbital Gyrus		
				medial superior occipital gyrus	Lateral occipital cortex		
				rostrodorsal area 40 (PFt)	IPL		
				rostroventral area 39 (PGa)			
				rostroventral area 40 (PFop)			
			caudal temporal thalamus	rostrodorsal area 40 (PFt)			
				rostroventral area 39 (PGa)			
			posterior parietal thalamus	rostrodorsal area 40 (PFt)			
				caudal area 40 (PFm)			
				rostroventral area 39 (PGa)			
				rostroventral area 40 (PFop)			
				lateral superior occipital gyrus			
				postcentral area 7	SPL		
				1rostral area 45	Orbital Gyrus		
				middle occipital gyrus	Inferior occipital gyrus		
				A4ul	Area 4upper limb region		
Right		IPL	caudal area 39 (PGp)	A38l, lateral area	STG		
		Precuneus	dmPOS, dorsomedial parietooccipital sulcus	A38l, lateral area			
				A22r, rostral area			

Table 3 | Parcel-to-parcel disconnections following the region-to-region disconnectivity analysis at *p* < .05.

4. Discussion

The present study evaluated how white matter disconnection affected arithmetic fact retrieval. We carried out two lesion-disconnection analyses in first-time stroke patients with unilateral damage to either the left or right hemisphere performing a multiplication task. In the first analysis, patients' lesions were superimposed to a white matter tractography map, leading to individual disconnection topographies (Griffis et al., 2019). A whole-brain univariate analysis

313   suggested that disconnection of white matter fibers situated between the anterior AG and
314   posterior STS was associated with a multiplication deficit. A second analysis was carried out
315   to investigate direct disconnections between two brain areas implicated in multiplication
316   deficits. Single brain areas were defined as ROIs by a connectivity-based grey matter atlas, and
317   disconnection between each pair of regions was investigated for its role in multiplication
318   deficits. We found several structures with multiple relevant disconnections. These included the
319   left thalamus, (intra)parietal areas such as the AG, STG, IFG, and occipital areas. Single
320   disconnections with the strongest disconnection-deficit association were found between the
321   thalamus and the IPS as well as occipital regions, but also between the primary auditory cortex
322   and occipital areas. Results of these analyses will be discussed in turn in the following.

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

324   The findings of the whole-brain analysis fit well with a connectivity approach of arithmetic
325   fact retrieval put forward by Klein et al. (2016). In this approach, connections between the
326   MTG and the AG were considered necessary for arithmetic fact retrieval, as both areas are
327   essential elements of a left-hemispheric arithmetic fact retrieval network. A significant role of
328   the AG for arithmetic fact retrieval has also been suggested by several neuropsychological
329   single case studies on arithmetic fact retrieval (e.g., Hittmair-Delazer et al., 1994; Lee, 2000;
330   Cohen et al., 2000). However, other single case studies have questioned the importance of the
331   AG within this network, as they reported patients presenting with a multiplication deficit
332   despite having a preserved AG (Cohen et al., 2000; Dehaene & Cohen, 1997; van Harskamp et
333   al., 2005; Zaunmueller et al., 2009). For example, patient ATH had severe difficulties verbally
334   solving multiplication problems while making only a few mistakes in subtraction (Cohen et al.,
335   2000). On the other hand, Van Harskamp & Cipolotto (2001) reported on a patient who did not
336   show a multiplication deficit, although damage to left parietal regions, including the AG,
337   occurred.

338   Given both the current results and more recent research, inconsistent results of single case
339   studies can be explained by the approach of Klein and colleagues (2016): The disconnection
340   cluster indicated by our analysis to be associated with arithmetic fact retrieval involved the left
341   arcuate fasciculus, the temporopontine tract and U-fibers between the AG and STS. This
342   observation suggests that disconnection of the AG with temporal areas, such as STS, STG, and
343   MTG seems to cause an arithmetic fact retrieval deficit. This expands the results of previous
344   studies indicating the detrimental effect of lesions to or disconnection of the AG. In this sense,

345   Klein et al. (2013b) re-evaluated a single case reported by Zaunmueller et al. (2009), focusing
346   on lesions to the patient's white matter compared to previous single case studies focusing on
347   lesions more on grey matter damage. While the lesion itself was in the basal ganglia, it also
348   incorporated white matter fibers that explicitly connect frontal areas with the AG, suggesting
349   that the patient could not retrieve arithmetic facts due to poor connectivity of the AG. Similarly,
350   Mihulowicz et al. (2014) conducted a voxel-based lesion behavior mapping study observing
351   that white matter lesions to superior parts of the superior lateral fasciculus (SLF II) impaired
352   arithmetic fact retrieval.

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

359   Importantly, neurofunctional evidence from healthy participants on learning complex
360   multiplication facts (e.g., Delazer et al., 2003, 2005; Ischebeck et al., 2006, 2007; Grabner et
361   al., 2009; Rickard et al., 2000; Zamarian et al., 2009) also indicates that the AG plays a crucial
362   role in arithmetic fact retrieval. Bloechle et al. (2016) evaluated fMRI signal before and after
363   multiplication training. They found a stronger fMRI signal in the AG when comparing trained
364   vs. untrained multiplication tasks after training only, but no difference in activation when
365   directly comparing the same multiplication problems across training (post- vs. pre-training).
366   Therefore, the authors suggested that the AG might act as a 'circuit breaker', coordinating
367   whether a task is to be solved purely via fact retrieval or whether a switch in strategy requiring
368   additional cognitive processing, such as calculation, is necessary.

369   This aspect provides a compelling explanation for patient FS's ability to multiply correctly
370   despite damage to parietal areas, including the AG: They were still able to recall multiplication
371   facts due to an intact temporal retrieval network and did not require the AG to switch from fact
372   retrieval to calculation. In the current study, most patients with an arithmetic fact retrieval
373   deficit also suffered from aphasia. Accordingly, they might have not been able to recall
374   phonologically stored arithmetic facts initially. When attempting to switch to a calculation-
375   based strategy, these patients were also slowed due to the disconnection of AG. Therefore, a
376   possible explanation for the given findings may be that when arithmetic fact retrieval fails, the

377   AG is involved in switching the strategy by which a task is solved. When it is disconnected or
378   damaged, this switch fails.

379   Region-to-Region Disconnectivity

380   Results of the second analysis indicate several disconnections between left-hemispheric areas,
381   which lead to deficits in arithmetic fact retrieval. When considering the analysis using the more
382   liberal threshold (Figure 3, Panel A), several disconnection-groupings were significant. First
383   off, there were several disconnections of the left thalamus with parietal areas. The thalamus is
384   involved in various cognitive processes, such as memory, language or mental set-shifting (see
385   Saalmann & Kastner; 2015 for an overview). It is also explicitly considered to be involved in
386   mental arithmetic (Arsalidou & Taylor, 2011; Johnson & Ojemann, 2000; Koyama et al.,
387   2020). In the more conservative threshold analysis, two of the three significant disconnections
388   were of the thalamus involved connections with the intraparietal sulcus (IPS).

389   There is a broad consensus that the IPS is involved in magnitude processing (for meta-analyses
390   see Arsalidou & Taylor, 2011; Arsalidou et al., 2018; Dehaene et al., 2003; Hawes et al., 2019).
391   Yet, arithmetic tasks are typically not solved exclusively by either arithmetic fact retrieval or
392   magnitude manipulations (i.e., calculations). Instead, they are solved by an adaptive interplay
393   between both (Klein et al., 2016). It thus seems possible that arithmetic fact retrieval deficits
394   following disconnection between the thalamus and the IPS reflect difficulties in switching
395   between and integrating fact retrieval and magnitude manipulation strategies as already argued
396   on the whole-brain level. As a general conclusion, the thalamus may be considered as a sort of
397   central relay of information between different cortical areas, receiving, coordinating and
398   transmitting information across the cortex. Therefore, it should not be surprising that
399   disconnection of such a vital structure with anatomical correlates associated with number
400   processing, such as left-hemispheric parietal areas, would lead to deficits in multiplication.

401   Our results showed several disconnections of the left IFG with left (parieto-)occipital areas.
402   While previous research reported essential connections between parietal regions, such as the
403   AG, and the IFG, the role of fronto-occipital connections in arithmetic has not been focussed
404   on so far. Yet, it is known that the IFG is connected with the parietal and occipital cortex via
405   the inferior fronto-occipital fasciculus (IFOF). This suggests that disconnection of certain parts
406   of the IFOF may also lead to arithmetic fact retrieval deficits. The EC/EmC system corresponds
407   to a rostral/anterior segment of the IFOF (Willmes et al., 2014) and is considered to be part of
408   a ventral pathway involved in arithmetic fact retrieval (Klein et al., 2016). More precisely,

409   Klein et al. (2013b) found that arithmetic tasks which can be solved via arithmetic fact retrieval

410   were associated with a ventral processing route. This route ranges from frontal regions, such

411   as the medial frontal gyrus to parietal regions, including the AG via the middle longitudinal

412   fascicle (MdLF), which itself is part of the EC/EmC system. They suggested that this

413   connection serves the purpose of phonological or semantic access, similar to language

414   processes (e.g., Saur et al., 2008; Weiller et al., 2011). Therefore, in the current study, the

415   observed disconnections might have led to language-related errors, such as semantic or

416   phonemic paraphasias.

417   Finally, we observed several disconnections of the STG associated with an arithmetic fact

418   retrieval deficit. Most of these disconnections were to the SPL, more specifically, the

419   precuneus. This observation fits well with a series of fMRI studies in healthy adults (Prado et

420   al., 2011) as well as children with and without mathematical learning disabilities (e.g.,

421   Berteletti et al., 2011; Demir et al., 2014) that suggest that the STG, as well as the MTG play

422   a role in arithmetic fact retrieval. Similarly, the more conservative threshold analysis also found

423   a disconnection between the primary auditory cortex and the ventromedial parietooccipital

424   sulcus to be associated with impaired arithmetic fact retrieval. These connections have been

425   suggested to run via the MdLF, emphasizing its importance in the arithmetic fact retrieval

426   network.

427   The role of the AG in arithmetic fact retrieval

428   Taken together, the current results indicate that arithmetic fact retrieval is subserved by a

429   widespread left-hemispheric network including the AG, superior temporal gyrus, and the

430   thalamus, among others, thus corroborating the network suggested by Klein et al. (2016). In

431   particular, the first analysis corroborated the idea that the angular gyrus plays a central role in

432   arithmetic fact retrieval (e.g., Delazer et al., 2003; Dehaene et al., 2003) as a disconnection of

433   the AG led to impaired arithmetic fact retrieval. However, the second analysis revealed that

434   not only AG connectivity but also connectivity of various other left-hemispheric areas,

435   including the IPS, seems to be necessary for the successful retrieval of arithmetic facts. As

436   regards the role of the AG in the fact retrieval network, we suggest that the AG may not be the

437   (sole) storage location of arithmetic facts. Instead, it may serve a more regulatory role within

438   the network, for instance, subserving semantic integration of concepts (Amalric & Dehaene,

439   2017; Price et al., 2015) or strategy switching (Bloechle et al., 2016). For instance, patients

440   who could not solve tasks via arithmetic fact retrieval may have had to switch to a different

441   strategy requiring increased magnitude processing (e.g., Dehaene et al., 2003; Klein et al.,

442   2016). If these processing routes to the IPS of either hemisphere were also disconnected (i.e.,

443   due to a lesion affecting both association and commissural fibers), patients might not have been

444   able to use this compensatory mechanism adequately. Consequentially, they committed errors

445   or took longer than the ten-second cut-off time to solve the task.

446

447   Conclusion

448   Our data on lesion-disconnection analyses in unilateral stroke patients suggest that a deficit in

449   arithmetic fact retrieval cannot be tracked to a single locus within the brain. Instead,

450   impairments in arithmetic fact retrieval seem to originate from disconnections of several areas

451   within a left-hemispheric network around the AG, thalamus, STS, STG and MTG and IFG. On

452   a more general level, our study underlines the relevance of future research, taking into account

453   grey matter integrity and white matter connectivity in numerical cognition and cognition in

454   general.

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References

Amalric, M., & Dehaene, S. (2016). Origins of the brain networks for advanced mathematics in expert mathematicians. *Proceedings of the National Academy of Sciences*, *113*(18), 4909-4917.

Amalric, M., & Dehaene, S. (2017). Cortical circuits for mathematical knowledge: evidence for a major subdivision within the brain's semantic networks. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 373(1740), 20160515.

Amalric, M., & Dehaene, S. (2019). A distinct cortical network for mathematical knowledge in the human brain. *NeuroImage*, 189, 19-31.

Arsalidou, M., Pawliw-Levac, M., Sadeghi, M., & Pascual-Leone, J. (2018). Brain areas associated with numbers and calculations in children: Meta-analyses of fMRI studies. *Developmental Cognitive Neuroscience*, 30, 239-250.

Arsalidou, M., & Taylor, M. J. (2011). Is 2+ 2= 4? Meta-analyses of brain areas needed for numbers and calculations. *Neuroimage*, *54*(3), 2382-2393.

Biniek, R., Huber, W., Glindemann, R., Willmes, K., & Klumm, H. (1992). The Aachen Aphasia Bedside Test--criteria for validity of psychologic tests. *Der Nervenarzt*, *63*(8), 473-479.

Bloechle, J., Huber, S., Bahnmueller, J., Rennig, J., Willmes, K., Cavdaroglu, S., ... & Klein, E. (2016). Fact learning in complex arithmetic—the role of the angular gyrus revisited. *Human Brain Mapping*, *37*(9), 3061-3079.

Brant-Zawadzki, M., Atkinson, D., Detrick, M., Bradley, W. G., & Scidmore, G. (1996). Fluid-attenuated inversion recovery (FLAIR) for assessment of cerebral infarction: initial clinical experience in 50 patients. *Stroke*, 27(7), 1187-1191.

Cohen, L., Dehaene, S., Chochon, F., Lehericy, S., & Naccache, L. (2000). Language and calculation within the parietal lobe: a combined cognitive, anatomical and fMRI study. *Neuropsychologia*, *38*(10), 1426-1440.

de Haan, B., Clas, P., Juenger, H., Wilke, M., & Karnath, H. O. (2015). Fast semi-automated lesion demarcation in stroke. *NeuroImage: Clinical*, 9, 69-74.

Dehaene, S., & Cohen, L. (1995). Towards an anatomical and functional model of number processing. *Mathematical cognition*, 1(1), 83-120.

Dehaene, S., & Cohen, L. (1997). Cerebral pathways for calculation: Double dissociation between rote verbal and quantitative knowledge of arithmetic. Cortex, 33(2), 219-250.

Dehaene, S., Piazza, M., Pinel, P., & Cohen, L. (2003). Three parietal circuits for number processing. Cognitive neuropsychology, 20(3-6), 487-506.

506   Delazer, M., Domahs, F., Bartha, L., Brenneis, C., Lochy, A., Trieb, T., & Benke, T. (2003).
507   Learning complex arithmetic—an fMRI study. *Cognitive Brain Research*, *18*(1), 76-88.
508
509   Delazer, M., Ischebeck, A., Domahs, F., Zamarian, L., Koppelstaetter, F., Siedentopf, C. M.,
510   Kaufmann, L., Benke, T., & Felber, S. (2005). Learning by strategies and learning by drill—
511   evidence from an fMRI study. *Neuroimage*, *25*(3), 838-849.
512
513   Delazer, M., Zamarian, L., Benke, T., Wagner, M., Gizewski, E. R., & Scherfler, C. (2019).
514   Is an intact hippocampus necessary for answering 3× 3?–Evidence from Alzheimer's disease.
515   *Brain and cognition*, *134*, 1-8.
516
517   Fan, L., Li, H., Zhuo, J., Zhang, Y., Wang, J., Chen, L., ... & Jiang, T. (2016). The human
518   brainnetome atlas: a new brain atlas based on connectional architecture. *Cerebral cortex*,
519   *26*(8), 3508-3526.
520
521   Gauthier, L., Dehaut, F., & Joanette, Y. (1989). The bells test: a quantitative and qualitative
522   test for visual neglect. *International journal of clinical neuropsychology*, *11*(2), 49-54.
523
524   Grabner, R. H., Ansari, D., Koschutnig, K., Reishofer, G., Ebner, F., & Neuper, C. (2009a).
525   To retrieve or to calculate? Left angular gyrus mediates the retrieval of arithmetic facts
526   during problem solving. *Neuropsychologia*, *47*(2), 604-608.
527
528   Grabner, R. H., Ischebeck, A., Reishofer, G., Koschutnig, K., Delazer, M., Ebner, F., &
529   Neuper, C. (2009b). Fact learning in complex arithmetic and figural-spatial tasks: The role of
530   the angular gyrus and its relation to mathematical competence. *Human brain mapping*, *30*(9),
531   2936-2952.
532
533   Griffis, J. C., Metcalf, N. V., Corbetta, M., & Shulman, G. L. (2019). Structural
534   disconnections explain brain network dysfunction after stroke. *Cell reports*, *28*(10), 2527-
535   2540.
536
537   Griffis, J. C., Metcalf, N. V., Corbetta, M., & Shulman, G. L. (2021). Lesion Quantification
538   Toolkit: A MATLAB software tool for estimating grey matter damage and white matter
539   disconnections in patients with focal brain lesions. *NeuroImage: Clinical*, 102639.
540
541   Hawes, Z., Sokolowski, H. M., Ononye, C. B., & Ansari, D. (2019). Neural underpinnings of
542   numerical and spatial cognition: An fMRI meta-analysis of brain regions associated with
543   symbolic number, arithmetic, and mental rotation. *Neuroscience & Biobehavioral Reviews*,
544   103, 316-336.
545
546   Hittmair-Delazer, M., Semenza, C., & Denes, G. (1994). Concepts and facts in calculation.
547   *Brain*, *117*(4), 715-728.
548
549   Ischebeck, A., Zamarian, L., Siedentopf, C., Koppelstätter, F., Benke, T., Felber, S., &
550   Delazer, M. (2006). How specifically do we learn? Imaging the learning of multiplication and
551   subtraction. *Neuroimage*, *30*(4), 1365-1375.
552
553   Ischebeck, A., Zamarian, L., Egger, K., Schocke, M., & Delazer, M. (2007). Imaging early
554   practice effects in arithmetic. *Neuroimage*, *36*(3), 993-1003.
555

556 Johannsen, L., & Karnath, H. O. (2004). How efficient is a simple copying task to diagnose
557 spatial neglect in its chronic phase?. *Journal of Clinical and Experimental Neuropsychology*,
558 *26*(2), 251-256.

559 Johnson, M. D., & Ojemann, G. A. (2000). The role of the human thalamus in language and
560 memory: evidence from electrophysiological studies. *Brain and cognition*, *42*(2), 218-230.
561
562 Kalbe, E., Reinhold, N., Brand, M., Markowitsch, H. J., & Kessler, J. (2005). A new test
563 battery to assess aphasic disturbances and associated cognitive dysfunctions—German
564 normative data on the aphasia check list. *Journal of clinical and experimental*
565 *neuropsychology*, *27*(7), 779-794.
566
567 Klein, E., Bahnmueller, J., Mann, A., Pixner, S., Kaufmann, L., Nuerk, H. C., & Moeller, K.
568 (2013a). Language influences on numerical development—Inversion effects on multi-digit
569 number processing. *Frontiers in Psychology*, *4*, 480.
570
571 Klein, E., Moeller, K., Glauche, V., Weiller, C., & Willmes, K. (2013b). Processing pathways
572 in mental arithmetic—evidence from probabilistic fiber tracking. *PloS one*, *8*(1), e55455.
573
574 Klein, E., Moeller, K., & Willmes, K. F. (2013c). A neural disconnection hypothesis on
575 impaired numerical processing. *Frontiers in human neuroscience*, *7*, 663.
576
577 Klein, E., Suchan, J., Moeller, K., Karnath, H. O., Knops, A., Wood, G., ... & Willmes, K.
578 (2016). Considering structural connectivity in the triple code model of numerical cognition:
579 differential connectivity for magnitude processing and arithmetic facts. *Brain Structure and*
580 *Function*, *221*(2), 979-995.
581
582 Klein, E., Willmes, K., Bieck, S. M., Bloechle, J., & Moeller, K. (2019). White matter neuro-
583 plasticity in mental arithmetic: Changes in hippocampal connectivity following arithmetic
584 drill training. *Cortex*, *114*, 115-123.
585
586 Koyama, M. S., Molfese, P. J., Milham, M. P., Mencl, W. E., & Pugh, K. R. (2020).
587 Thalamus is a common locus of reading, arithmetic, and IQ: Analysis of local intrinsic
588 functional properties. *Brain and Language*, 209, 104835.
589
590 Lee, K. M. (2000). Cortical areas differentially involved in multiplication and subtraction: a
591 functional magnetic resonance imaging study and correlation with a case of selective
592 acalculia. *Annals of Neurology: Official Journal of the American Neurological Association*
593 *and the Child Neurology Society*, *48*(4), 657-661.
594
595 McCloskey, M., Aliminosa, D., & Sokol, S. M. (1991). Facts, rules and procedures in normal
596 calculation: Evidence from multiple single-patient studies of impaired arithmetic fact
597 retrieval. *Brain and cognition*, *17*(2), 154-203.
598
599 Mihulowicz, U., Willmes, K., Karnath, H. O., & Klein, E. (2014). Single-digit arithmetic
600 processing—anatomical evidence from statistical voxel-based lesion analysis. *Frontiers in*
601 *human neuroscience*, *8*, 286.
602
603 Moeller, K., Willmes, K., & Klein, E. (2015). A review on functional and structural brain
604 connectivity in numerical cognition. *Frontiers in human neuroscience*, *9*, 227.

Noguchi, K., Ogawa, T., Inugami, A., Fujita, H., Hatazawa, J., Shimosegawa, E., ... & Seto, H. (1997). MRI of acute cerebral infarction: a comparison of FLAIR and T2-weighted fast spin-echo imaging. *Neuroradiology*, 39(6), 406-410.

Nichols, T. E., & Holmes, A. P. (2002). Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Human brain mapping*, 15(1), 1-25.

Prado, J., Mutreja, R., Zhang, H., Mehta, R., Desroches, A. S., Minas, J. E., & Booth, J. R. (2011). Distinct representations of subtraction and multiplication in the neural systems for numerosity and language. *Human brain mapping*, *32*(11), 1932-1947.

Price, A. R., Bonner, M. F., Peelle, J. E., Grossman, M. (2015) Converging evidence for the neuroanatomic basis of combinatorial semantics in the angular gyrus. *J Neurosci* 35, 3276 – 3284.

Price, C. J. (2012). A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. *Neuroimage*, *62*(2), 816-847.

Ricci, P. E., Burdette, J. H., Elster, A. D., & Reboussin, D. M. (1999). A comparison of fast spin-echo, fluid-attenuated inversion-recovery, and diffusion-weighted MR imaging in the first 10 days after cerebral infarction. *American journal of neuroradiology*, 20(8), 1535-1542.

Rickard, T. C., Romero, S. G., Basso, G., Wharton, C., Flitman, S., & Grafman, J. (2000). The calculating brain: an fMRI study. *Neuropsychologia*, *38*(3), 325-335.

Rorden, C., Bonilha, L., Fridriksson, J., Bender, B., & Karnath, H. O. (2012). Age-specific CT and MRI templates for spatial normalization. *Neuroimage*, 61(4), 957-965.

Rorden, C., & Karnath, H. O. (2010). A simple measure of neglect severity. *Neuropsychologia*, *48*(9), 2758-2763.

Saalmann, Y. B., & Kastner, S. (2015). The cognitive thalamus. *Frontiers in systems neuroscience*, 9, 39.

Saur, D., Kreher, B. W., Schnell, S., Kümmerer, D., Kellmeyer, P., Vry, M. S., ... & Weiller, C. (2008). Ventral and dorsal pathways for language. *Proceedings of the national academy of Sciences*, 105(46), 18035-18040.

Schaefer, P. W., Hunter, G. J., He, J., Hamberg, L. M., Sorensen, A. G., Schwamm, L. H., ... & Gonzalez, R. G. (2002). Predicting cerebral ischemic infarct volume with diffusion and perfusion MR imaging. *American Journal of Neuroradiology*, 23(10), 1785-1794.

van Harskamp, N. J., & Cipolotti, L. (2001). Selective impairments for addition, subtraction and multiplication. Implications for the organization of arithmetical facts. *Cortex*, *37*(3), 363-388.

Van Harskamp, N. J., Rudge, P., & Cipolotti, L. (2005). Cognitive and social impairments in patients with superficial siderosis. *Brain*, *128*(5), 1082-1092.

655 Weber, J., Mattle, H. P., Heid, O., Remonda, L., & Schroth, G. (2000). Diffusion-weighted
656 imaging in ischaemic stroke: a follow-up study. *Neuroradiology*, 42(3), 184-191.

658 Weiller, C., Bormann, T., Saur, D., Musso, M., & Rijntjes, M. (2011). How the ventral
659 pathway got lost–And what its recovery might mean. *Brain and language*, 118(1-2), 29-39.

661 Weintraub, S. (1985). Mental state assessment of young and elderly adults in behavioral
662 neurology. *Principles of behavioral neurology*, 71-123.

664 Willmes, K., Moeller, K., & Klein, E. (2014). Where numbers meet words: a common ventral
665 network for semantic classification. *Scandinavian journal of psychology*, 55(3), 202-211.

667 Yeh, F. C., Panesar, S., Fernandes, D., Meola, A., Yoshino, M., Fernandez-Miranda, J. C., ...
668 & Verstynen, T. (2018). Population-averaged atlas of the macroscale human structural
669 connectome and its network topology. *NeuroImage*, *178*, 57-68.

671 Zamarian, L., Ischebeck, A., & Delazer, M. (2009). Neuroscience of learning arithmetic—
672 evidence from brain imaging studies. *Neuroscience & Biobehavioral Reviews*, *33*(6), 909-
673 925.

675 Zaunmüller, L., Domahs, F., Dressel, K., Lonnemann, J., Klein, E., Ischebeck, A., &
676 Willmes, K. (2009). Rehabilitation of arithmetic fact retrieval via extensive practice: a
677 combined fMRI and behavioural case-study. *Neuropsychological Rehabilitation*, *19*(3), 422-
678 443.

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