Effective Connectivity of the Multiplication Network: A Functional MRI and Multivariate Granger Causality Mapping Study

Frank Krueger,[1*†] Steffen Landgraf,[2,3,4†] Elke van der Meer,[2] Gopikrishna Deshpande,[5] and Xiaoping Hu[5]

[1]*Department of Molecular Neuroscience, George Mason University, Fairfax*
[2]*Department of Psychology, Humboldt University, Berlin, Germany*
[3]*University Pierre and Marie Curie, Paris VI, France*
[4]*Center for Psychiatry and Neuroscience, INSERM U894, Sainte Anne Hospital, Paris, France*
[5]*Department of Biomedical Engineering, Emory University and Georgia Institute of Technology, Atlanta, Georgia*

Abstract: Developmental neuropsychology and functional neuroimaging evidence indicates that simple and complex mental calculation is subserved by a fronto-parietal network. However, the effective connectivity (connection direction and strength) among regions within the fronto-parietal network is still unexplored. Combining event-related fMRI and multivariate Granger Causality Mapping (GCM), we administered a multiplication verification task to healthy participants asking them to solve single and double-digit multiplications. The goals of our study were first, to identify the effective connectivity of the multiplication network, and second, to compare the effective connectivity patterns between a low and a high arithmetical competence (AC) group. The manipulation of multiplication difficulty revealed a fronto-parietal network encompassing bilateral intraparietal sulcus (IPS), left pre-supplementary motor area (PreSMA), left precentral gyrus (PreCG), and right dorsolateral prefrontal cortex (DLPFC). The network was driven by an intraparietal IPS-IPS circuit hosting a representation of numerical quantity intertwined with a fronto-parietal DLPFC-IPS circuit engaged in temporary storage and updating of arithmetic operations. Both circuits received additional inputs from the PreCG and PreSMA playing more of a supportive role in mental calculation. The high AC group compared to the low AC group displayed a greater activation in the right IPS and based its calculation more on a feedback driven intraparietal IPS-IPS circuit, whereas the low competence group more on a feedback driven fronto-parietal DLPFC-IPS circuit. This study provides first evidence that multivariate GCM is a sensitive approach to investigate effective connectivity of mental processes involved in mental calculation and to compare group level performances for different populations. *Hum Brain Mapp 32:1419–1431, 2011.* © 2010 Wiley-Liss, Inc.

Key words: calculation; connectivity; dorsolateral prefrontal cortex; intraparietal sulcus; mathematical competence; Granger causality

[†]These authors contributed equally to this work.

Contract grant sponsor: Georgia Research Alliance; Contract grant sponsor: NIH; Contract grant number: EB002009.

*Correspondence to: Frank Krueger, Ph.D., Department of Molecular Neuroscience, Krasnow Institute for Advanced Study, George Mason University, 4400 University Drive, MSN: 1G3, Fairfax, VA 22030. E-mail: fkrueger@gmu.edu

Received for publication 23 July 2009; Revised 2 June 2010; Accepted 4 June 2010

DOI: 10.1002/hbm.21119

Published online 16 August 2010 in Wiley Online Library (wileyonlinelibrary.com).

INTRODUCTION

Over the last decade, significant progress has been made in uncovering the neural basis of mathematical reasoning. Evidence from primate neurophysiology, brain-damage patients, human functional neuroimaging, and developmental neuropsychology indicates that performance in simple and complex mental calculation is subserved by a fronto-parietal network [Ansari, 2008]. The performance in both simple and complex mental calculation is subserved by a fronto-parietal network [Dehaene et al., 2003]. Within the parietal cortex, the tripartite framework for number processing proposes a reproducible set of three parietal brain regions that are systematically involved in mental calculation [Dehaene et al., 2003]. The bilateral intraparietal sulcus (IPS) is systematically recruited in number tasks and probably hosts a quantity system, in which numerical quantity is represented in a language-independent format [Dehaene et al., 1999; Molko, 2003; Rickard et al., 2000]. The left angular gyrus (AG) is involved in linguistically mediated operations in mental calculation such as the retrieval of overlearned arithmetic facts (e.g., multiplication tables) [Delazer et al., 2004; Grabner et al., 2007, 2008]. The bilateral posterior superior parietal lobe (PSPL) is engaged in number manipulation but is not specific to the number domain and likely supports attentional orientation to the mental number line [Dehaene et al., 2003; Menon et al., 2000; Pesenti et al., 2000].

Within the frontal cortex, the dorsolateral prefrontal cortex (DLPFC), precentral gyrus (PreCG), and pre-supplementary motor area (PreSMA) play a more supportive role of successive multi-component cognitive functions including mathematical operations, retrieving arithmetic facts, and carrying out supporting arithmetic operations during mental calculation [Ansari, 2008]. The DLPFC has been implicated in sequential ordering of operations [Kazui et al., 2000; Rickard et al., 2000], working memory demands [Aleman and van't Wout, 2008; Kazui et al., 2000; Menon et al., 2000], strategic organization [Rickard et al., 2000], and rule updating of mathematical operations [Montojo and Courtney, 2008]. The left PreCG has been associated in aspects of numerical knowledge [Dehaene et al., 1996; Gruber et al., 2001], such as the concept of ordinarity, large and small number comparisons, and the development of a number line. The PreSMA has been linked to processes supporting operation procedures [Kong et al., 2005].

A plethora of functional neuroimaging studies have demonstrated the implication of this fronto-parietal network in mathematical thinking [e.g., Sohn et al., 2004], complex calculation [e.g., Zago et al., 2001], calculation expertise [e.g., Pesenti et al., 2001], mathematical competences [e.g., Grabner et al., 2007], and integral calculus [e.g., Krueger et al., 2008]. In addition, recent neuroimaging studies indicate a shift in brain activation from frontal to more parietal regions with arithmetic training [Delazer et al., 2003, 2005; Ischebeck et al., 2006, 2007] and age [Rivera et al., 2005] for solving mathematical problems. Finally, a recent neuroimaging study revealed that adults with higher mathematical competence displayed stronger activation in the left AG of the parietal cortex while solving arithmetic problems, demonstrating a stronger reliance on automatic, language-mediated processes in more competent individuals [Grabner et al., 2007]. However, little is known about the effective connectivity (direction and strength of connections) among brain regions within the fronto-parietal network and how effective connectivity patterns of brain regions differ based on mathematical competence.

In the present study, we combined a slow event-related fMRI design with a multivariate Granger Causality Mapping (GCM) analysis while administering a multiplication verification task to healthy participants asking them to solve easy, moderate, and difficult multiplication tasks. The goals of our study were two-fold. First, we aimed to identify the multiplication network underlying varying multiplication difficulty and to determine the effective connectivity among its brain regions. We hypothesized that varying multiplication task difficulty will be subserved by a fronto-parietal network, which will be driven by the interplay of an intraparietal circuit supporting math-specific operations and a fronto-parietal circuit supporting math-supportive operations. Second, we aimed to compare effective connectivity patterns of the multiplication network between a low and a high arithmetic competence group. We hypothesized a shift from the frontal to the parietal cortex for brain activation and effective connectivity patterns in the high compared to the low competence group.

METHODS

Subjects

Twenty neurologically healthy right-handed volunteers [eight females, 12 males, years of age (Mean $\pm$ SD): 26.1 $\pm$ 6.7, years of education: 14.9 $\pm$ 1.8] were selected for this study from a larger pool based on their performance on the arithmetic intelligence (A-IQ) subscale (Mean = 100; SD = 15) of the well-established German Intelligence-Structure-Test (I-S-T 2000 R) [Amthauer et al., 2000]. The A-IQ score was calculated based on the sum raw score of three subtests: number sequence completion (e.g., 2; 5; 8; 11; 14; 17; 20; ?); non-verbal arithmetic problem solving (e.g., 15 + H = 25 − H; H?); and algebraic sign completion (e.g., 121 ? 10 ? 8 = 888). We subdivided the entire group (A-IQ: 107.6 $\pm$ 2.6) into a low (n = 10, 92.4 $\pm$ 2.3) and a high (n = 10, 122.7 $\pm$ 2.9) arithmetic competence (AC) group by a median split. Subgroups differed in A-IQ [$t(18) = -8.14$, $P < 0.001$], but not in age [$t(18) = -1.40$, $P = 0.179$], education [$t(18) = -0.37$, $P = 0.714$], or gender [$\chi^2(1) = 0.789$, $P = 0.650$]. Participants gave their informed written consent prior to examination that was approved by the local ethical committee.

Task

The fMRI experiment consisted of a multiplication verification task, in which the prime stimulus was a multiplication problem (e.g., 4×7) and the target stimuli were two candidate answers (e.g., $28 = 38$). Participants were asked to select the correct answer by pressing either the index or middle finger of their right hand. Task difficulty was manipulated in a factorial design with three levels by varying the number of operands: easy (E, one-digit times one-digit, e.g., 6×7), moderate (M, two-digit times one-digit, e.g., 12×8), and difficult (D, two-digit times two-digit, e.g., 19×12). Factors in tasks ranged from 4 to 9 for the E condition, 4 to 19 for the M condition, and 12 to 19 for the D condition. Note that 10 as a factor and ties (e.g., 9×9, 12×12) were excluded. The two candidate answers always consisted of the correct result and a number that was 10 units off avoiding false answer rejection by fast strategies such as size approximation or last digit inspection.

Each trial began with a presentation of a fixation point in the middle of the screen (0.5 s) followed by the prime stimulus also appearing in the middle of the screen (1 s). Then, another fixation point was presented (1 s), before the two candidate answers were presented to the left and right side of the center of the screen. Participants were asked to select the correct answer by pressing either the index (left) or middle finger (right) of their right hand (time limit 12 s). After participants' responses, a blank screen appeared for the remaining time and was followed by a jittered interstimulus interval (3.5 s).

Before entering the scanner, participants were familiarized with the task using a separate set of stimuli. During the experiment, participants had to respond as quickly and accurately as possible. Response times (RT) and error rates (ER) were recorded for each of the 36 pseudo-randomized trials (12 per difficulty condition). The fMRI measurement consisted of one experimental run taking ~12 min. After the fMRI experiment, participants judged each multiplication task's difficulty on a nine-point Likert rating scale (Rating, RAT; 1 = easy; 9 = difficult).

Data Acquisition

Imaging was performed on a 1.5 Tesla Siemens Vision whole-body scanner (Siemens, Erlangen, Germany). Anatomical (T1-weighted 3D MP-RAGE sequence: TR, 9.7 ms; TE, 4.0 ms; flip angle, 12°; number of slices, 190; FOV, 256 mm; matrix size, 256×256; voxel size, $1 \times 1 \times 1$ mm^3) and functional images (2D gradient EPI sequence: TR, 2 s; TE, 60 ms; flip angle, 90°; thickness, 5 mm; number of slices, 16; FOV, 210 mm; matrix size, 64×64) were acquired. Altogether 407 volume images were taken parallel to the AC-PC line. The first five volumes were discarded to allow for T1 equilibration effects. Head motion was restricted using foam pads placed around the participant's head. Stimulus presentation was synchronized with the scanner data acquisition using the ERTS (Experimental Run Time System, Berisoft Cooperation, Germany) software package. With a magnetically shielded LCD video projector, stimuli were back-projected onto a translucent screen. Participants viewed the screen via a mirror system attached to the head coil. The resulting visual angle for stimuli was ~2°.

Data Analysis

Behavioral data analyses were carried out using SPSS 14.0 (SPSS, Chicago) with alpha set to $P < 0.05$. Behavioral data were normally distributed (Kolmogorov–Smirnov test) and assumptions for analyses of variance (Bartlett's test) were not violated. Behavioral data (RT, ER, RAT) were analyzed using a two-way repeated-measure ANOVA with Difficulty (E, M, D) as a within-subject factor and Group (low AC, high AC) as a between-subject factor. Functional data analyses were performed using BrainVoyager QX (Brain Innovation, Maastricht, The Netherlands). Preprocessing of the functional data included slice-scan time correction (sinc interpolation), small head movements correction by spatially aligning all volumes to the first volume (rigid body transformation), removal of linear trends and low frequency non-linear drifts of three or fewer cycles for the time series (temporal high-pass filtering), and spatial smoothing of the functional images (Gaussian filter of 12 mm FWHM). Preprocessing of the anatomical data included reassembling into 1 mm resolution and normalizing into Talairach space using a piecewise linear transformation. Functional data were co-registered with the individual's 3D anatomical images and then reassembled into $3 \times 3 \times 3$ mm^3 isotropic voxels.

A General Linear Model (GLM) corrected for first-order serial correlation was applied [Friston et al., 1999]. Random-effect analyses were performed on the multi-subject level ($n = 20$) to explore brain regions that were associated with levels of multiplication difficulty. The GLM model consisted of a set of three regressors (E, M, D). The regressor time courses were adjusted for the hemodynamic response delay by convolution with a double-gamma hemodynamic response function [Buchel et al., 1998]. Multiple regression analyses were performed independently for the time course of each individual voxel. After computing the coefficients (parameter estimates) for all regressors, t tests were performed between coefficients resulting from the three conditions. A statistical model on the multi-subject level was fit for a (pseudo-parametric) difficulty contrast ($D > M \cap M > E$) to explore brain activity that monotonically increased with task difficulty during solving multiplication problems. The conjunction of these two contrasts ($D > M$, $M > E$) provides the specificity about the coded linear parametric effect, requiring a significant effect in each of these contrasts ("minimum t statistic") [Nichols et al., 2005].

In addition, an ROI analysis was performed to explore group differences between the low and high competence groups. In particular, parameter estimates (mean beta weights) for each condition (E, M, D) were derived from each brain region of the identified difficulty circuitry after determining the peak of activation and surrounding voxels encompassing a cube of 243 mm^3. Those parameter estimates were averaged and entered into a two-way repeated-measure ANOVA with Difficulty (E, M, D) as a within-subject factor and Group (low AC, high AC) as a between-subject factor.

The cluster-level statistical threshold approach was used to correct for multiple comparisons by calculating the minimum cluster size to achieve a false activation probability $\alpha = 0.05$. This approach is based on a 3D extension of the randomization procedure described in Forman et al. [1995]. First, the voxel-level threshold was set at $t(19) = 3.86$ ($P < 0.001$, uncorrected) for the difficulty contrast. Afterwards, the thresholded map was submitted to a whole-brain correction criterion based on the estimate of the map's spatial smoothness and on an iterative procedure (Monte Carlo simulation) for estimating cluster level false-positive rates. The implemented method corrects for multiple cluster tests across space. For each simulated image, all "active" clusters in the imaged volume are considered and used to update a table reporting the counts of all the clusters above this threshold for each specific size. After 1,000 iterations, an alpha value is assigned to each cluster size based on its observed relative frequency. From this information the minimum cluster size threshold is specified to yield a cluster-level false-positive rate of $\alpha = 5\%$. The estimated minimum cluster size of 380 mm^3 was applied to the statistical map for the difficulty contrast. Clusters that exceeded this minimum cluster size were used to create functional ROIs.

Time courses of each condition were extracted from each ROI to compute their respective percentage signal changes with the condition-per-file-based series as baseline. Brodmann areas (BA) were determined by using the Talairach Daemon Client software (Research Imaging Center, San Antonio, TX) and the co-planar stereotaxic atlas of the human brain [Talairach and Tournoux, 1988]. Statistical images were overlaid onto a surface brain map in Talairach space.

Multivariate Granger Causality Analysis

The Granger causality concept draws on the principle of temporal predictability [Granger, 1969] assuming that if the current temporal progression of brain activity in one brain region allows the prediction of future temporal progression of activity in another brain region, then the first brain region is assumed to have a causal influence on the second brain region. Effective connectivity was implemented using a multivariate GCM analysis [Kaminski et al., 2001] that was based on a multivariate vector autoregessive (MVAR) model capable of capturing the simultaneous directional influences between multiple ROIs without any a priori assumptions about the underlying fronto-parietal network [Deshpande et al., 2008, 2009; Kus et al., 2004]. A critical methodological aspect of the GCM method is how the multiple ROIs are determined. Since any selection criterion runs the risk of excluding regions that actually contribute to the network, a stringent approach was used and only those ROIs that increased with task difficulty and survived the initial difficulty contrast in our fMRI analysis were selected for the subsequent GCM analysis. The ROIs were constrained to the center of activation within each ROI and to a maximum size of $5 \times 5 \times 5$ mm^3. The entire time series of blood oxygenation dependent (BOLD) signal intensities from the selected ROIs were averaged across voxels, then normalized across runs and subjects, and finally collapsed across all runs and subjects to obtain a single time series per ROI [Deshpande et al., 2008, 2009].

A first order MVAR model was fit based on the time series of selected ROIs and a directed transfer function (DTF) matrix was obtained [Kus et al., 2004]. The DTF matrix was weighted by the partial coherence between the selected ROIs in order to emphasize direct connections [Deshpande et al., 2008, 2009]. The order of the model was determined using Akaike Information Criterion [Akaike, 1974]. The DTF is based on the principle of Granger causality but is rendered in a multivariate framework and therefore can effectively model the inherently multivariate nature of neuronal networks [Blinowska et al., 2004]. This method has been validated previously using simulations [Kus et al., 2004] and applied successfully to electrophysiological [Blinowska et al., 2004; Ding et al., 2000; Kaminski et al., 2001; Korzeniewska et al., 2003; Kus et al., 2004] and fMRI data measuring the BOLD response [Deshpande et al., 2008, 2009; Stilla et al., 2007]. The DTF analysis matrix consists of a set of directional path weights describing the strength of mutual impact (in arbitrary units) from each ROI to each of the other ROIs. In addition, a direct comparison of the networks between the low and high competence groups was applied to investigate if groups based their calculation on different pathways. Surrogate null distributions were used to assess the significance of the path weights ($P < 0.05$) [Deshpande et al., 2008]. Since the selected ROIs survived multiple comparison corrections in the initial fMRI analyses, no further significance correction was applied [Stilla et al., 2007]. Bivariate correlations (Spearman's correlation) were computed between participants' A-IQ and effective connectivity data derived from the multivariate GCM analysis.

RESULTS

Behavioral Data

Descriptive statistics for RT, ER, and RAT for the difficulty conditions (E, M, D) are presented in Figure 1. Each of the two-way repeated-measures group ANOVAs on RT, ER, and RAT revealed a significant main effect for

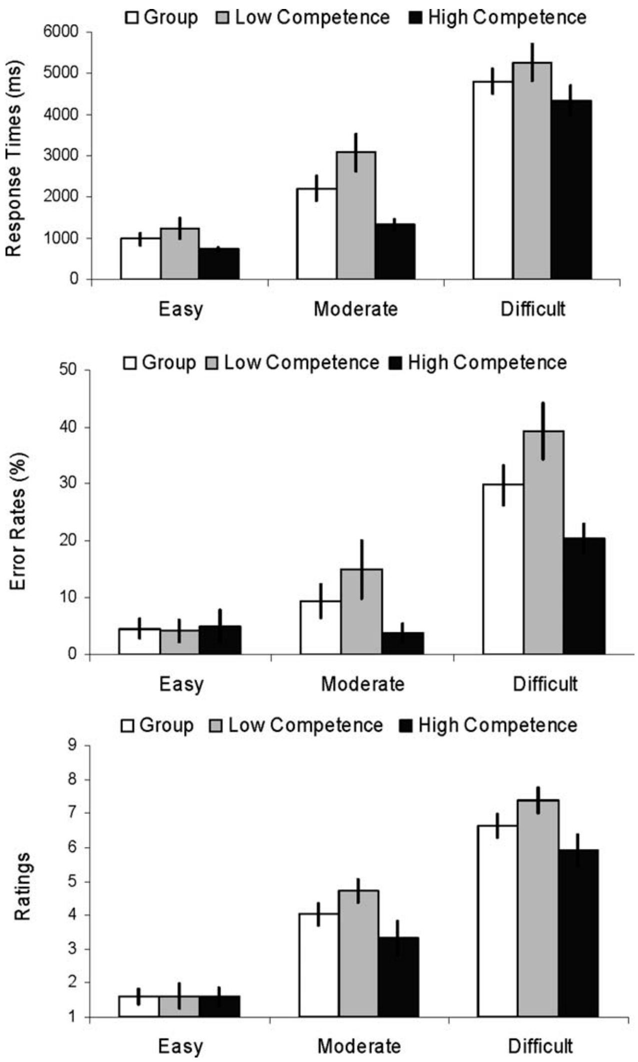

Figure 1.

Behavioral results. Descriptive statistics (Mean ± SEM) for response times, error rates, and ratings for the three difficulty conditions (easy, moderate, and difficult) are displayed for the entire group and the low and high arithmetic competence subgroups.

Difficulty [$F_{RT}(2,36) = 131.08$; $F_{ER}(2,36) = 58.11$; $F_{RAT}(2,36) = 277.02$, $Ps < 0.001$] and Group [$F_{RT}(1,18) = 8.97$; $F_{ER}(1,18) = 6.07$; $F_{RAT}(1,18) = 5.02$, $Ps < 0.05$]. Planned follow-up within-subject contrasts (Helmert-Method) showed that RT, ER, and RAT were lower in the easy compared to the moderate and difficult conditions [$F_{RT}(1,18) = 193.17$; $F_{ER}(1,18) = 40.02$; $F_{RAT}(1,18) = 277.30$, $Ps < 0.001$] as well as in the moderate compared to the difficult condition [$F_{RT}(1,18) = 92.16$; $F_{ER}(1,18) = 86.07$; $F_{RAT}(1,18) = 276.24$, $Ps < 0.001$]. In addition, each of the two-way repeated-measures subgroup ANOVAs on RT, ER, and RAT revealed a significant Group × Difficulty interaction effect [$F_{RT}(2,36) = 3.60$; $F_{ER}(2,36) = 7.97$; $F_{RAT}(2,36) = 7.29$, $Ps < 0.05$], indicating that the performance in RT, ER, and RAT differed from the easy to the difficult condition for the low AC group compared to the high AC group.

FMRI and Effective Connectivity Data

The difficulty contrast looking for increasing brain activity corresponding with multiplication difficulty revealed activation in a fronto-parietal network comprising the bilateral IPS (BA 40), left PreCG (BA 6), left PreSMA (BA 6), and right DLPFC (BA 9) (Fig. 2, Table I). Note that the reverse contrast yielded no brain activation. To explore group difference between the low and high AC groups, an ROI analysis was performed by entering the mean parameter estimates from each region of the difficulty circuitry into a two-way repeated-measure ANOVA with Difficulty (E, M, D) as a within-subject factor and Group (low AC, high AC) as a between-subject factor. The analyses revealed a significant main effect for Difficulty for each brain region of the difficulty circuitry [Left IPS: $F(2,36) = 51.66$, Right IPS: $F(2,36) = 61.35$, PreCG: $F(2,36) = 126.37$, PreSMA: $F(2,36) = 95.38$, DLPFC: $F(2,36) = 56.89$; $Ps < 0.001$], but no significant Group × Difficulty interaction effects. Importantly, a significant main effect for Group was found in the right IPS [$F(1,18) = 6.35$; $P < 0.05$]. Planned follow-up independent-samples t tests showed that the brain activation in the right IPS for the high AC group compared to the low AC group was greater across all conditions [E: $t(18) = 2.95$; M: $t(18) = 2.64$; D: $t(18) = 2.77$; $Ps < 0.05$].

On the basis of the multivariate GCM analysis, effective connectivity patterns among aforementioned brain regions were derived and significant paths are displayed for the entire group (Fig. 3a) and separately for the low and high AC groups (Fig. 3b). Note that for the displayed paths a pseudo-color code was used to indicate the path weights of all connections between ROIs. In addition, path weights for all connections are given in Table II where the direction of influence is from the columns to the rows. The arrows beside each path weight indicate whether the target ROI's BOLD response had the tendency to vary with that of the source ROI's BOLD response, albeit with a phase difference, in the same direction (↑) or the opposite direction (↓) [Stilla et al., 2007].

For the entire group, the difficulty multiplication network was driven by the left hemisphere that gave more outputs ($n = 4$) to than received inputs ($n = 1$) from the right hemisphere. Inter-hemispherically, the right and left IPS were reciprocally connected within the parietal cortex, whereas the PreCG and PreSMA gave unidirectional outputs to the right DLPFC within the frontal cortex. Intra-hemispherically, the IPS and the DLPFC were reciprocally connected within the right hemisphere, whereas the PreCG was reciprocally connected with the IPS and the PreSMA in the left hemisphere. The parietal cortex received more inputs ($n = 4$) than it produced outputs ($n = 2$) through both uni- and bidirectional paths from the frontal cortex. The left PreSMA emerged as the strongest driver in the network, being the only region that had outputs to all

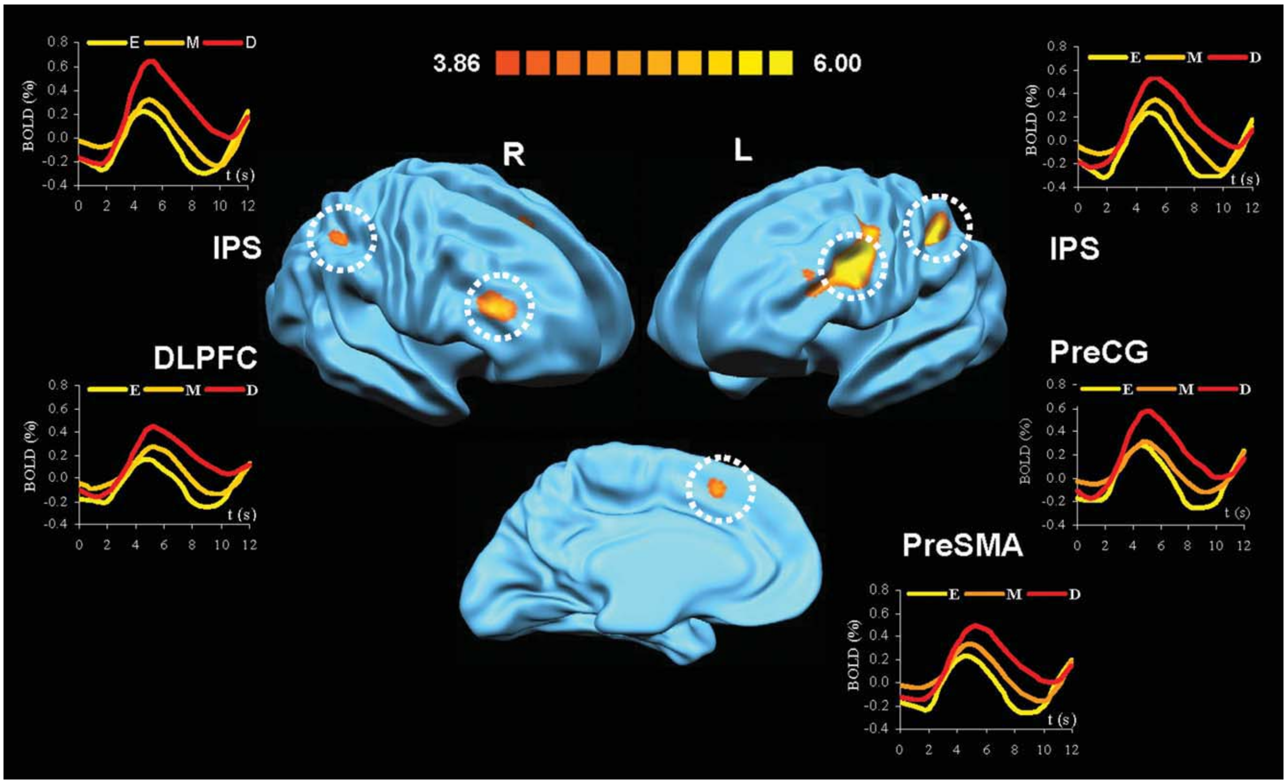

Figure 2.

Brain activations. Brain regions for the multiplication network that were activated with increasing task difficulty are displayed: bilateral intraparietal sulcus (IPS), left pre-supplementary motor area (PreSMA), left precentral gyrus (PreCG), and right dorsolateral prefrontal cortex (DLPFC). Time courses of activation profiles for each brain region. *X*-axis, post-stimulus onset times measured from prime stimulus onsets. *Y*-axis, adjusted BOLD signal changes expressed in relative percentage of the mean. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

other brain regions in the fronto-parietal network. For the subgroups, the connectivity patterns for the multiplication networks largely overlapped. Importantly, the low AC group based its calculation more on a right intra-hemispheric circuit between the reciprocally fronto-parietally connected DLPFC and IPS (P [(R IPS→R DLPFC)$_{low}$–(R IPS→R DLPFC)$_{high}$] = 0.011). In contrast, the high AC group based its calculation more on an inter-hemispheric circuit between the reciprocally connected right and left IPS (P [(R IPS→L IPS)$_{high}$–(R IPS→L IPS)$_{low}$] = 0.002, P [(L IPS→R IPS)$_{high}$–(L IPS→R IPS)$_{low}$] = 0.004). The strength of the left-right IPS connection correlated significantly with A-IQ (r = 0.49, P < 0.05), indicating that the higher the arithmetic competence the stronger the effective connectivity between both IPS regions.

DISCUSSION

In the present study, we combined event-related fMRI and multivariate GCM while administering a multiplication

TABLE I. Brain activations for the multiplication difficulty network

Regions of activation*	Laterality	Talairach coordinates *x*	*y*	*z*	Cluster size (mm^3)	t(19) peak$^{\#}$
Intraparietal Sulcus (BA 40, IPS)	R	33	−49	42	435	4.04
Intraparietal Sulcus (BA 40, IPS)	L	−33	−46	40	5,999	5.43
Pre-Supplementary Motor Area (BA 6, PreSMA)	L	−9	14	46	585	4.56
Precentral Gyrus (BA 6, PreCG)	L	−36	5	28	13,325	6.10
Dorsolateral Prefrontal Cortex (BA 9, DLPFC)	R	39	26	28	4,074	4.64

*BA, Brodmann area;
$^{\#}P$ < 0.05 (cluster-level threshold corrected).

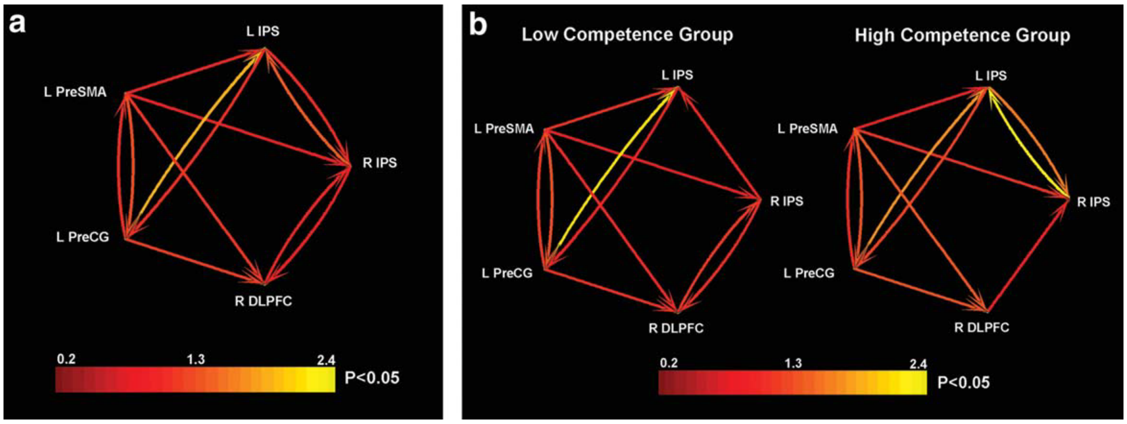

Figure 3.
Multivariate Granger causality mapping analysis. Effective connectivity networks are displayed for (**a**) the entire group and (**b**) the low and high arithmetic competence groups. Those networks only display the significant connections ($P < 0.05$). R, right; L, left; IPS, intraparietal sulcus; Pre-SMA, pre-supplementary motor area; PreCG, precentral gyrus; DLPFC, dorsolateral prefrontal cortex. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

verification task to healthy participants asking them to solve single and double-digit multiplications. The goal of our study was twofold: First, we aimed to identify the hypothesized fronto-parietal multiplication network underlying varying multiplication difficulty and to determine the effective connectivity among its brain regions and assumed that the network will be driven by the interplay of an intraparietal circuit supporting math-specific operations and a fronto-

TABLE II. Path weights for the networks as shown in Figure 3

	R IPS	L IPS	L PreSMA	L PreCG	R DLPFC
Entire group (n = 20)					
R IPS	0	**0.521**↑	**0.331**↑	0.009↑	**0.440**↑
L IPS	**1.043**↑	0	**0.471**↑	**1.813**↑	0.001↑
L PreSMA	0.021↓	0.145↓	0	**0.582**↑	0.085↑
L PreCG	0	**0.560**↑	**0.901**↑	0	0.172↑
R DLPFC	**0.263**↑	0.015↓	**0.632**↑	**0.741**↑	0
Low arithmetic competence group (n = 10)					
R IPS	0	0.120↓	**0.221**↑	0.048↑	**0.592**↑
L IPS	**0.393**↑	0	**0.521**↑	**2.141**↑	0.003↑
L PreSMA	0.140↓	0.160↓	0	**0.612**↑	0.123↑
L PreCG	0.003↑	**0.315**↑	**0.832**↑	0	0.146↑
R DLPFC	**0.481**↑	0.012↓	**0.416**↑	**0.526**↑	0
High arithmetic competence group (n = 10)					
R IPS	0	**1.267**↑	**0.553**↑	0.004↑	**0.222**↑
L IPS	**2.310**↑	0	**0.304**↑	**1.482**↑	0.001↑
L PreSMA	0.141↑	0.124↓	0	**0.511**↑	0.020↓
L PreCG	0.001↑	**0.755**↑	**0.926**↑	0	0.152↑
R DLPFC	0.021↑	0.013↓	**0.942**↑	**0.924**↑	0

R, right; L, left; IPS, intraparietal sulcus; PreSMA, pre-supplementary motor area; PreCG, precentral gyrus; DLPFC, dorsolateral prefrontal cortex.
Note that path weights for all significant connections are marked in bold. Analogous to positive and negative correlations, the arrows beside each path weight reflect the tendency of the BOLD signal in the two ROIs linked by the path: "covarying" paths (↑) to covary either in the same direction (i.e., both tending to increase or decrease together albeit with a phase difference) or "antivarying" paths (↓) to vary in opposite directions (i.e., one tending to increase when the other tends to decrease).

parietal circuit supporting math-supportive operations. Second, we aimed to compare both brain activation and effective connectivity patterns of the identified multiplication network between a low and a high arithmetic competence group and assumed a shift from frontal to more parietal regions for the high competence group in brain activation and effective connectivity while solving complex multiplication.

With respect to our first goal, we identified the underlying brain activation and effective connectivity of the multiplication network. The manipulation of multiplication difficulty recruited a fronto-parietal network encompassing the bilateral IPS, left PreCG, left PreSMA, and right DLPFC. Our fMRI results are in line with previous studies confirming the role of those brain regions in mental multiplication [Dehaene and Cohen, 1995; Dehaene et al., 2003] and other calculation tasks where task complexity was varied [Gruber et al., 2001; Kong et al., 2005; Menon et al., 2000; Zago et al., 2001]. The manipulation of multiplication difficulty did not reveal activations in the bilateral PSPL and left AG. Although the PSPL is engaged in number manipulation, those regions are not specific to the number domain and are more likely to support attentional orientation to the mental number line [Dehaene et al., 2003; Menon et al., 2000; Pesenti et al., 2000]. The left AG is thought to be involved in linguistic processing [Dehaene et al., 2003], in which arithmetic operations require either verbal coding of numbers or draw on the automatic retrieval of verbally stored arithmetic facts (e.g., multiplication tables) [Dehaene et al., 2003; Menon et al., 2000; Simon et al., 2002]. In addition, the left AG is jointly involved by other language tasks such as digit naming [Zago et al., 2001] or phoneme detection [Simon et al., 2002]. The lack of activation in the left AG can be interpreted to reflect less reliance on automatic fact retrieval but instead more real-time calculation with increasing multiplication difficulty. The ability to perform complex multiplication requires the interplay of different math-specific and math-supportive cognitive processes including retrieval of arithmetic facts but also access to numerical meaning as well as carrying out mathematical operations and supporting arithmetic operations [Ashcraft, 1992; McCloskey et al., 1985]. For example, a task like 12×8 might be solved by decomposing the task in the following way: $12 \times 8 = 10 \times 8 + 2 \times 8 = 80 + 16 = 96$. To solve even more complex multiplication tasks (e.g., 12×14), additional mathematical and supporting arithmetic operations are necessary requiring longer solution times and might lead to higher error rates. The behavioral results in our study confirmed that task difficulty ratings increased with number of operations and led to longer solution times and higher error rates.

Importantly, the multivariate GCM analysis allowed determining the direction and strength of connections between the identified brain regions. Within the parietal cortex, the activations of the left and right IPS regions corresponded to a previous meta-analysis of magnitude representation [Cohen Kadosh et al., 2008] and formed an inter-hemispheric reciprocally connected circuit that hosts a representation of quantity [Dehaene et al., 1999; Rickard et al., 2000], which is always present in both hemispheres. This is compatible with the observation that numerical comparison is accessible to both hemispheres in split-brain patients [Cohen and Dehaene, 1996; Seymour et al., 1994]. Right IPS disorganization [Temple and Marriott, 1998], structural IPS abnormalities in Turner's syndrome [Molko et al., 2003], and left IPS gray matter loss in children with dyscalculia [Isaacs et al., 2001] are all associated with abnormal arithmetic processing. The IPS circuit is systematically involved in numerals whether they are spoken or written or whether they appear in Arabic notation or in spelled-out form [Eger et al., 2003; Le Clec et al., 2000; Naccache and Dehaene, 2001; Piazza et al., 2002; Pinel et al., 2001]. This circuit is modulated by semantic parameters such as absolute magnitude of numbers or their value relative to a reference point [Dehaene et al., 2003]. Its involvement lasts longer during operations with greater numbers compared to small numbers [Kiefer and Dehaene, 1997; Stanescu-Cosson et al., 2000]. Finally, the engagement of the right IPS increases with task difficulty, for example, when individuals have to compute two operations instead of one [Menon et al., 2000].

The task difficulty sensitive right IPS formed an extra intra-hemispherically reciprocally connected circuit with the right DLPFC, fitting with the assumption that numerosity is first computed in the parietal cortex, then transmitted and kept online by DLPFC activity for further operations [Nieder and Miller, 2004]. Brain-imaging studies of single-or multi-digit calculation in healthy adults report activations within the DLPFC that are based either on phonological or visuo-spatial manipulations in working memory [Delazer et al., 2003, 2005; Gruber et al., 2001; Pesenti et al., 2001; Zago et al., 2001]. We speculate that an increase in multiplication difficulty diminishes the dependence on automatic fact retrieval and elicits more visuo-spatial instead of phonological manipulation in working memory. For example, participants might have solved the multiplication tasks (especially for the moderate and difficult problems) by imagining the written multiplication algorithm where numbers are written underneath each other. A recent fMRI study investigated the respective contributions of verbal and/or spatial working memory manipulation brain networks during mathematical calculation and demonstrated that the right DLPFC and parietal cortex are elicited by number and locations manipulation tasks for spatial working memory and attentional processes [Zago et al., 2008]. Our observed right DLPFC activation is also consistent with neuroimaging studies of spatial selective attention including shifts of spatial attention [Behrmann et al., 2004; Corbetta et al., 1998; Hillis et al., 2000; Wojciulik and Kanwisher, 1999], spatial working memory [Wager and Smith, 2003], and spatial mental imagery [Mellet et al., 1998]. In particular, it has been shown that number processing via spatial working memory requires a functional interaction between inferior parietal cortex and right DLPFC [Kazui et al., 2000; Rickard et al., 2000]. The right DLPFC received additional unilateral inputs from the left PrecCG and left PreSMA supporting its engagement in temporary storage, sequential ordering, and updating of arithmetic operations in more complex [Gruber et al., 2001; Zago et al., 2001] and previously untrained calculations [Burbaud et al., 1995; Dehaene et al., 1996; Ischebeck et al., 2007].

Within the frontal cortex, the left PreSMA and left PreCG were reciprocally connected and emerged as key components of the multiplication network, confirming their intrinsic involvement in other multiplication and addition tasks [Chochon et al., 1999; Dehaene et al., 1996; Pesenti et al., 2000]. In particular, the PreSMA was the only region with outputs to all other regions in the fronto-parietal network, providing further evidence for its involvement in supporting operating procedures during more difficult mental calculations [Kong et al., 2005]. The PreCG was another strong driver in the multiplication network. Based on its proximity to the primary motoric finger areas, it is considered to be a part of a finger-movement network that may underlie finger-counting as a basic numerical learning strategy when arithmetic skills are first spontaneously acquired [Butterworth, 1999; Carpenter and Moser, 1983; Fuson, 1988; Geary, 2000]. The PreCG was also reciprocally connected with the IPS, supporting the argument that the internal quantification representation of numerical knowledge in the PreCG might develop from external finger digit manipulation during finger-counting over time [Simon, 1999], leading to its co-activation with the bilateral IPS during additions [Pesenti et al., 2000; Stanescu-Cosson et al., 2000], multiplications [Dehaene et al., 1996; Zago et al., 2001], and subtractions [Rueckert et al., 1996]. Several additional lines of evidence suggest a close relationship between number and finger representations including developmental [e.g., Butterworth, 2000; Fayol et al., 1998], behavioral [Di Luca et al., 2006; Goldin-Meadow and Wagner, 2005], neuropsychological [e.g., Gerstmann, 1927; Mayer et al., 1999], and transcranial magnetic stimulation [e.g., Andres et al., 2007; Sato et al., 2007] data. This derived finger counting strategy, developed during numerical acquisition in childhood to represent, manipulate, and communicate numbers, is still automatically evoked by adults during number processing.

With respect to our second goal, we compared both brain activation and effective connectivity patterns of the identified multiplication network between a low and a high arithmetic competence group. The low and high competence group demonstrated only activation differences in the right IPS during solving multiplication problems, indicating that the activation for the high competence group compared to the low competence group was greater across all types of multiplication problems. Therefore, the high competence group based its calculation more on a feedback driven inter-hemispheric intraparietal circuit between the reciprocally connected right IPS and left IPS, whereas the low competence group on a feedback driven right intra-hemispheric fronto-parietal circuit between the reciprocally connected DLPFC and IPS.

For the low competence group, the reliance on the fronto-parietal DLPFC-IPS circuit indicated a more effortful multi-step calculation integration process. Our behavioral results confirmed performance differences in terms of ratings, response times, and error rates with increasing task difficulty between the low and high competence groups. We suggest that during complex multiplication, numerosity is computed in the bilateral IPS, then transmitted forward and backward within the fronto-parietal DLPFC-IPS circuit, and kept online by the DLPFC for updating mathematical operations and carrying out supporting arithmetic operations. A recent study revealed that the neural systems engaged in updating of mathematical operations (i.e., rules) and numbers in working memory are dissociable [Montojo and Courtney, 2008]. Specifically, updating of mathematical operations (i.e., rules) preferentially activates the prefrontal cortex, whereas updating of numbers preferentially activates the parietal cortex. Further evidence demonstrated that number processing via spatial working memory requires a functional interaction between inferior parietal cortex and right DLPFC [Kazui et al., 2000; Rickard et al., 2000], in which the DLPFC serves as a top-down control unit [Corbetta and Shulman, 2002; Krueger et al., 2007]. Finally, it has been demonstrated that repetitive transcranial magnetic stimulation over the right DLPFC interferes with digit span performance implying a critical role of this region in subserving short-term retention [Aleman and van't Wout, 2008]. Our results support the idea that complex multiplication is intertwined in a functional fronto-parietal interaction between the bilateral IPS and the right DLPFC, which can be differently recruited based on mathematical competence.

For the high competence group, the reliance upon the IPS-IPS circuit indicates a shift from frontal to more parietal regions for solving complex multiplication confirming existing evidence based on development, training, and competence of arithmetic skills. First, functional neuroimaging evidence demonstrated that neurodevelopmental changes in mental arithmetic leads to a functional fronto-parietal neuroanatomy shift [Rivera et al., 2005]. Older individuals showed a greater activation in the left parietal cortex, along the supramarginal gyrus and the adjacent anterior IPS as well as the left lateral occipital temporal cortex. In contrast, younger individuals revealed greater activation in the prefrontal cortex (PFC) including the dorsolateral and ventrolateral PFC and the anterior cingulate cortex, suggesting that they require comparatively more working memory and attentional resources to achieve similar levels of mental arithmetic performance. Similar evidence for a fronto-parietal shift with age has been shown for more basic tasks such as symbolic [Ansari et al., 2005; Kaufmann et al., 2006] and non-symbolic magnitude comparison [Ansari and Dhital, 2006].

Second, recently a series of fMRI studies investigated the acquisition of arithmetic skills by comparing brain activation during previously trained problems to activation during untrained problems [Delazer et al., 2003, 2005; Ischebeck et al., 2006, 2007]. Overall, the comparison between trained and untrained problems demonstrated a shift from frontal activations in untrained to more parietal activations in trained problems. In addition, a shift within the parietal lobe from the IPS in untrained problems to the left AG in trained problems has been reported. These observations were interpreted to represent a shift from a more calculation-related retrieval of the result to a more language-related retrieval rooted in semantic long-term memory.

Finally, a recent neuroimaging study investigated whether the brain activation during mental calculation is modulated by individual differences in mathematical competence [Grabner et al., 2007]. Adults were divided into a low and high mathematical competence groups based on their performance on standardized arithmetic tests. During an fMRI block-design, participants were asked to verify the correctness of single-digit and multi-digit multiplication problems. The results demonstrated that adults with higher mathematical competence displayed stronger activation in the left AG while solving arithmetic problems. The authors argue that the recruitment of the left AG suggests a stronger reliance on automatic, language-mediated processes in more competent individuals.

The finding by Grabner et al. [2007] seems to contradict our findings that the recruitment of the right IPS during arithmetic problem solving underlies individual differences in mathematical competence. However, we argue that the observed differences in brain regions might be explained by different designs in both experiments. First, different math competence tests were used to define the arithmetic competence groups. Whereas Grabner et al. [2007] applied a self-constructed test on multiplication performance (consisting of one-digit times one-digit and one-digit times two-digit multiplication problem) similar to the task types applied in the fMRI experiment, we administrated the A-IQ subscale of the normed I-S-T 2000 R (consisting of number sequence completion, non-verbal arithmetic problem solving, and algebraic sign completion) [Amthauer et al., 2000]. Since our competence test relies more on quantity-based numerical processes than on fact retrieval as measured by the test of Grabner et al. [2007], this might explain the demonstrated competence effect in right IPS rather than in the left AG during mental multiplication problem solving.

Second, Grabner et al. [2007] used multiplication problems varying two levels of arithmetic difficulty (i.e., one-digit times one-digit versus one-digit times two-digit or two-digit times one-digit) similar to other arithmetic training neuroimaging studies [e.g., Delazer et al., 2003; Ischebeck et al., 2006, 2007], whereas we applied multiplication problems with three levels of arithmetic difficulty (i.e., one-digit times one-digit, one-digit times two-digit or two-digit times one-digit, and two-digit times two-digit). If both the solutions of one-digit times one-digit and two-digit times one-digit problems (e.g., $8 \times 9 = 72$ and $12 \times 6 = 72$) rely on fact retrieval, then one would expect no differences in behavioral measures (e.g., response times, error rates, or difficulty ratings) for both task types. However, in our study we found differences for all three measures between one-digit times one-digit, two-digit times one-digit, and two-digit times two-digit problems. In our opinion, the solving of multiplication problems with increasing difficulty requires the interplay of different cognitive math-specific and math-supportive functions such as access to numerical meaning as well as carrying out mathematical and supporting arithmetic operations besides fact retrieval [Ashcraft, 1992; McCloskey et al., 1985]. Hence, activation in the left AG might be more associated with language-related components of overlearned high arithmetic competence as shown by Grabner et al. [2007]. In contrast, our study demonstrates that the right IPS and its effective connectivity to the left IPS might be more involved in high arithmetic competence necessary for real-time mathematical computations that strongly rely on processes mediating the representation of numerical quantity. Importantly, the strength of connection between the left and right IPS correlated significantly with arithmetic competence, indicating that the higher the arithmetic competence the stronger the effective connectivity between both IPS regions. Moreover, in a recent study we used the same stimuli to investigate cognitive resource allocation for neural activity underlying mathematical cognition combing fMRI and pupillometry measuring pupil dilation as an indicator for cognitive resource allocation or processing load [Landgraf et al., in press]. The results revealed that behavioral and pupil dilation data increased parametrically with task difficulty and pupil dilation was sensitive to cognitive resource allocation for neural activity underlying math-specific cognition in the bilateral intraparietal sulcus, implicating a strong reliance on numerical quantity processing during multiplication. However, further research is needed to investigate the relationship between individual differences in sub-components of arithmetic competence and the underlying neural circuits of arithmetic problem solving.

CONCLUSION

The present study provides first evidence that individuals with higher arithmetic competence based their calculation more on a feedback driven intraparietal IPS-IPS circuit to solve single and double-digit multiplication, suggesting a stronger reliance on math-specific processes mediating the representation of numerical quantity. In contrast, individuals with lower arithmetic competence based their calculation more on a feedback driven fronto-parietal DLPFC-IPS circuit, suggesting a stronger reliance on processes mediating math-supportive operations such as updating of mathematical operations and math-specific operations such as updating of numbers. On a broader level, combining fMRI and multivariate GCM is a sensitive approach to investigate the effective connectivity of mental processes involved in calculation and to compare group level performances for different populations. Its application might lead to a better understanding of dynamical changes in arithmetic abilities as a function of development, training, and expertise. Considering the interactions among regions involved in brain networks in addition to localization of function in selected regions in healthy adults could potentially lead to useful insights into learning disabilities such as dyscalculia, and guide rehabilitation attempts with appropriate intervention programs [Krueger and Grafman, 2008].

REFERENCES

Akaike H (1974): A new look at the statistical model identification. IEEE Trans Automatic Control 19:716–723.

Aleman A, van't Wout M (2008): Repetitive transcranial magnetic stimulation over the right dorsolateral prefrontal cortex disrupts digit span task performance. Neuropsychobiology 57:44–48.

Amthauer R, Brocke B, Liepmann D, Beauducel A (2000): Intelligenz-Struktur-Test 2000 R. Goettingen: Hogrefe-Verlag.

Andres M, Seron X, Olivier E (2007): Contribution of hand motor circuits to counting. J Cogn Neurosci 19:563–576.

Ansari D (2008): Effects of development and enculturation on number representation in the brain. Nat Rev Neurosci 9:278–291.

Ansari D, Dhital B (2006): Age-related changes in the activation of the intraparietal sulcus during nonsymbolic magnitude processing: An event-related functional magnetic resonance imaging study. J Cogn Neurosci 18:1820–1828.

Ansari D, Garcia N, Lucas E, Hamon K, Dhital B (2005): Neural correlates of symbolic number processing in children and adults. Neuroreport 16:1769–1773.

Ashcraft MH (1992): Cognitive arithmetic: A review of data and theory. Cognition 44:75–106.

Behrmann M, Geng JJ, Shomstein S (2004): Parietal cortex and attention. Curr Opin Neurobiol 14:212–217.

Blinowska KJ, Kus R, Kaminski M (2004): Granger causality and information flow in multivariate processes. Phys Rev E Stat Nonlin Soft Matter Phys 70 (5 Part 1):050902.

Buchel C, Holmes AP, Rees G, Friston KJ (1998): Characterizing stimulus-response functions using nonlinear regressors in parametric fMRI experiments. Neuroimage 8:140–148.

Burbaud P, Degreze P, Lafon P, Franconi JM, Bouligand B, Bioulac B, Caille JM, Allard M (1995): Lateralization of prefrontal activation during internal mental calculation: A functional magnetic resonance imaging study. J Neurophysiol 74:2194–2200.

Butterworth B (1999): A head for figures. Science 284:928–929.

Butterworth B (2000): The Mathematic Brain. London: Macmillan.

Carpenter TP, Moser JM (1983): The aquisition of addition and subtraction concepts. In: Lesh R, Landau M, editors. Acquisition of Mathematics L Concepts and Processses. New York: Academic Press. pp 7–44.

Chochon F, Cohen L, van de Moortele PF, Dehaene S (1999): Differential contributions of the left and right inferior parietal lobules to number processing. J Cogn Neurosci 11:617–630.

Cohen Kadosh R, Lammertyn J, Izard V (2008): Are numbers special? An overview of chronometric, neuroimaging, developmental and comparative studies of magnitude representation. Prog Neurobiol 84:132–147.

Cohen L, Dehaene S (1996): Cerebral networks for number processing: Evidence from a case of posterior callosal lesion. Neurocase 2:155–174.

Corbetta M, Akbudak E, Conturo TE, Snyder AZ, Ollinger JM, Drury HA, Linenweber MR, Petersen SE, Raichle ME, Van Essen DC (1998): A common network of functional areas for attention and eye movements. Neuron 21:761–773.

Corbetta M, Shulman GL (2002): Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 3:201–215.

Dehaene S, Cohen L (1995): Towards an anatomical and functional model of number processing. Math Cogn 1:83–120.

Dehaene S, Piazza M, Pinel P, Cohen L (2003): Three parietal circuits for number processing. Cogn Neuropsychol 20:487–506.

Dehaene S, Spelke E, Pinel P, Stanescu R, Tsivkin S (1999): Sources of mathematical thinking: Behavioral and brain-imaging evidence. Science 284:970–974.

Dehaene S, Tzourio N, Frak V, Raynaud L, Cohen L, Mehler J, Mazoyer B (1996): Cerebral activations during number multiplication and comparison: A PET study. Neuropsychologia 34:1097–1106.

Delazer M, Domahs F, Bartha L, Brenneis C, Lochy A, Trieb T, Benke T (2003): Learning complex arithmetic-an fMRI study. Brain Res Cogn Brain Res 18:76–88.

Delazer M, Domahs F, Lochy A, Bartha L, Brenneis C, Trieb T (2004): The acquisition of arithmetic knowledge—An FMRI study. Cortex 40:166–167.

Delazer M, Ischebeck A, Domahs F, Zamarian L, Koppelstaetter F, Siedentopf CM, Kaufmann L, Benke T, Felber S (2005): Learning by strategies and learning by drill: Evidence from an fMRI study. Neuroimage 25:838–849.

Deshpande G, Hu X, Stilla R, Sathian K (2008): Effective connectivity during haptic perception: A study using Granger causality analysis of functional magnetic resonance imaging data. Neuroimage 40:1807–1814.

Deshpande G, Laconte S, James GA, Peltier S, Hu X (2009): Multivariate Granger causality analysis of fMRI data. Hum Brain Mapp 30:1361–1373.

Di Luca S, Grana A, Semenza C, Seron X, Pesenti M (2006): Finger-digit compatibility in Arabic numeral processing. Q J Exp Psychol (Colchester) 59:1648–1663.

Ding M, Bressler SL, Yang W, Liang H (2000): Short-window spectral analysis of cortical event-related potentials by adaptive multivariate autoregressive modeling: Data preprocessing, model validation, and variability assessment. Biol Cybern 83:35–45.

Eger E, Sterzer P, Russ MO, Giraud AL, Kleinschmidt A (2003): A supramodal number representation in human intraparietal cortex. Neuron 37:719–725.

Fayol M, Barrouillet P, Marinthe C (1998): Predicting arithmetical achievement from neuro-psychological performance: A longitudinal study. Cognition 68:B63–B70.

Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC (1995): Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): Use of a cluster-size threshold. Magn Reson Med 33:636–647.

Friston KJ, Holmes AP, Worsley KJ (1999): How many subjects constitute a study? NeuroImage 10:1–5.

Fuson KC (1988): Children's Counting and Concepts of Number. New York: Springer.

Geary DC (2000): From infancy to adulthood: The development of numerical abilities. Eur Child Adolesc Psychiatry 9 (Suppl 2):II11–II16.

Gerstmann J (1927): Fingeragnosie and isolierte Agraphie: Eine Neues Syndrom. Z Ges Neurol Psychat 108:152–177.

Goldin-Meadow S, Wagner SM (2005): How our hands help us learn. Trends Cogn Sci 9:234–241.

Grabner RH, Ansari D, Koschutnig K, Reishofer G, Ebner F, Neuper C (2009): To retrieve or to calculate? Left angular gyrus mediates the retrieval of arithmetic facts during problem solving. Neuropsychologia 47:604–608.

Grabner RH, Ansari D, Reishofer G, Stern E, Ebner F, Neuper C (2007): Individual differences in mathematical competence predict parietal brain activation during mental calculation. Neuroimage 38:346–356.

Granger C (1969): Investigating causal relations by econometric models and cross-spectral methods. Econometrica 37:424–438.

Gruber O, Indefrey P, Steinmetz H, Kleinschmidt A (2001): Dissociating neural correlates of cognitive components in mental calculation. Cereb Cortex 11:350–359.

Hillis AE, Barker PB, Beauchamp NJ, Gordon B, Wityk RJ (2000): MR perfusion imaging reveals regions of hypoperfusion associated with aphasia and neglect. Neurology 55:782–788.

Isaacs EB, Edmonds CJ, Lucas A, Gadian DG (2001): Calculation difficulties in children of very low birthweight: A neural correlate. Brain 124 (Part 9):1701–1707.

Ischebeck A, Zamarian L, Egger K, Schocke M, Delazer M (2007): Imaging early practice effects in arithmetic. Neuroimage 36:993–1003.

Ischebeck A, Zamarian L, Siedentopf C, Koppelstatter F, Benke T, Felber S, Delazer M (2006): How specifically do we learn? Imaging the learning of multiplication and subtraction. Neuroimage 30:1365–1375.

Kaminski M, Ding M, Truccolo WA, Bressler SL (2001): Evaluating causal relations in neural systems: granger causality, directed transfer function and statistical assessment of significance. Biol Cybern 85:145–157.

Kaufmann L, Koppelstaetter F, Siedentopf C, Haala I, Haberlandt E, Zimmerhackl LB, Felber S, Ischebeck A (2006): Neural correlates of the number-size interference task in children. Neuroreport 17:587–591.

Kazui H, Kitagaki H, Mori E (2000): Cortical activation during retrieval of arithmetical facts and actual calculation: A functional magnetic resonance imaging study. Psychiatry Clin Neurosci 54:479–485.

Kiefer M, Dehaene S (1997): The time course of parietal activation in single-digit multiplication: Evidence from event-related potentials. Math Cogn 3:1–30.

Kong J, Wang C, Kwong K, Vangel M, Chua E, Gollub R (2005): The neural substrate of arithmetic operations and procedure complexity. Brain Res Cogn Brain Res 22:397–405.

Korzeniewska A, Manczak M, Kaminski M, Blinowska KJ, Kasicki S (2003): Determination of information flow direction among brain structures by a modified directed transfer function (dDTF) method. J Neurosci Methods 125:195–207.

Krueger F, Fischer R, Heinecke A, Hagendorf H (2007): An fMRI investigation into the neural mechanisms of spatial attentional selection in a location-based negative priming task. Brain Res 1174:110–119.

Krueger F, Grafman J (2008): Disorders of mathematics: Implications for adult functioning. In: Lorraine E, Schreiber LE, Wasserstein J, editors. Adult Learning Disorders: Contemporary Issues. New York, NY: Psychology Press. pp 191–218.

Krueger F, Spampinato MV, Pardini M, Pajevic S, Wood JN, Weiss GH, Landgraf S, Grafman J (2008): Integral calculus problem solving: An fMRI investigation. Neuroreport 19:1095–1099.

Kus R, Kaminski M, Blinowska KJ (2004): Determination of EEG activity propagation: Pair-wise versus multichannel estimate. IEEE Trans Biomed Eng 51:1501–1510.

Landgraf S, van der Meer E, Krueger F: Cognitive resource allocation for neuronal activity underlying mathematical cognition: A Multi-Method Study. Int J Math Ed. DOI: 10.1007/s11858-010-0264-7.

Le Clec HG, Dehaene S, Cohen L, Mehler J, Dupoux E, Poline JB, Lehericy S, van de Moortele PF, Le Bihan D (2000): Distinct cortical areas for names of numbers and body parts independent of language and input modality. Neuroimage 12: 381–391.

Mayer E, Martory MD, Pegna AJ, Landis T, Delavelle J, Annoni JM (1999): A pure case of Gerstmann syndrome with a subangular lesion. Brain 122 (Part 6):1107–1120.

McCloskey M, Caramazza A, Basili A (1985): Cognitive mechanisms in number processing and calculation: Evidence from dyscalculia. Brain Cogn 4:171–196.

Mellet E, Petit L, Mazoyer B, Denis M, Tzourio N (1998): Reopening the mental imagery debate: Lessons from functional anatomy. Neuroimage 8:129–139.

Menon V, Rivera SM, White CD, Glover GH, Reiss AL (2000): Dissociating prefrontal and parietal cortex activation during arithmetic processing. Neuroimage 12:357–365.

Molko N, Cachia A, Riviere D, Mangin JF, Bruandet M, Le Bihan D, Cohen L, Dehaene S (2003): Functional and structural alterations of the intraparietal sulcus in a developmental dyscalculia of genetic origin. Neuron 40:847–858.

Molko N, Cachia A, Riviere D, Mangin JF, Bruandet M, Le Bihan D, Cohen L, Dehaene S (2003): Functional and structural alterations of the intraparietal sulcus in a developmental dyscalculia of genetic origin. Neuron 40:847–858.

Montojo CA, Courtney SM (2008): Differential neural activation for updating rule versus stimulus information in working memory. Neuron 59:173–182.

Naccache L, Dehaene S (2001): The priming method: Imaging unconscious repetition priming reveals an abstract representation of number in the parietal lobes. Cereb Cortex 11:966–974.

Nichols T, Brett M, Andersson J, Wager T, Poline JB (2005): Valid conjunction inference with the minimum statistic. Neuroimage 25:653–660.

Nieder A, Miller EK (2004): A parieto-frontal network for visual numerical information in the monkey. Proc Natl Acad Sci USA 101:7457–7462.

Pesenti M, Thioux M, Seron X, De Volder A (2000): Neuroanatomical substrates of arabic number processing, numerical comparison, and simple addition: A PET study. J Cogn Neurosci 12:461–479.

Pesenti M, Zago L, Crivello F, Mellet E, Samson D, Duroux B, Seron X, Mazoyer B, Tzourio-Mazoyer N (2001): Mental calculation in a prodigy is sustained by right prefrontal and medial temporal areas. Nat Neurosci 4:103–107.

Piazza M, Mechelli A, Butterworth B, Price CJ (2002): Are subitizing and counting implemented as separate or functionally overlapping processes? Neuroimage 15:435–446.

Pinel P, Dehaene S, Riviere D, LeBihan D (2001): Modulation of parietal activation by semantic distance in a number comparison task. Neuroimage 14:1013–1026.

Rickard TC, Romero SG, Basso G, Wharton C, Flitman S, Grafman J (2000): The calculating brain: An fMRI study. Neuropsychologia 38:325–335.

Rivera SM, Reiss AL, Eckert MA, Menon V (2005): Developmental changes in mental arithmetic: Evidence for increased functional specialization in the left inferior parietal cortex. Cereb Cortex 15:1779–1790.

Rueckert L, Lange N, Partiot A, Appollonio I, Litvan I, Le Bihan D, Grafman J (1996): Visualizing cortical activation during mental calculation with functional MRI. Neuroimage 3:97–103.

Sato M, Cattaneo L, Rizzolatti G, Gallese V (2007): Numbers within our hands: Modulation of corticospinal excitability of hand muscles during numerical judgment. J Cogn Neurosci 19:684–693.

Seymour SE, Reuter-Lorenz PA, Gazzaniga MS (1994): The disconnection syndrome. Basic findings reaffirmed. Brain 117 (Part 1):105–115.

Simon O, Mangin JF, Cohen L, Le Bihan D, Dehaene S (2002): Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. Neuron 33:475–487.

Simon TJ (1999): The foundations of numerical thinking in a brain without numbers. Trends Cogn Sci 3:363–365.

Sohn MH, Goode A, Koedinger KR, Stenger VA, Fissell K, Carter CS, Anderson JR (2004): Behavioral equivalence, but not neural equivalence—Neural evidence of alternative strategies in mathematical thinking. Nat Neurosci 7:1193–1194.

Stanescu-Cosson R, Pinel P, van De Moortele PF, Le Bihan D, Cohen L, Dehaene S (2000): Understanding dissociations in dyscalculia: A brain imaging study of the impact of number size on the cerebral networks for exact and approximate calculation. Brain 123 (Part 11):2240–2255.

Stilla R, Deshpande G, LaConte S, Hu X, Sathian K (2007): Posteromedial parietal cortical activity and inputs predict tactile spatial acuity. J Neurosci 27:11091–11102.

Talairach J, Tournoux P (1988): Co-Planar Stereotaxic Atlas of the Human Brain. New York: Thieme Medical Publishers.

Temple CM, Marriott AJ (1998): Arithmetic ability and disability in Turner's syndrome: A cognitive neuropsychological analysis. Dev Neuropsychol 14:47–67.

Wager TD, Smith EE (2003): Neuroimaging studies of working memory: A meta-analysis. Cogn Affect Behav Neurosci 3:255–274.

Wojciulik E, Kanwisher N (1999): The generality of parietal involvement in visual attention. Neuron 23:747–764.

Zago L, Pesenti M, Mellet E, Crivello F, Mazoyer B, Tzourio-Mazoyer N (2001): Neural correlates of simple and complex mental calculation. Neuroimage 13:314–327.

Zago L, Petit L, Turbelin MR, Andersson F, Vigneau M, Tzourio-Mazoyer N (2008): How verbal and spatial manipulation networks contribute to calculation: An fMRI study. Neuropsychologia 46:2403–2414.