

Virtual Dyscalculia Induced by Parietal-Lobe TMS Impairs Automatic Magnitude Processing

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Summary

People suffering from developmental dyscalculia encounter difficulties in automatically accessing numerical magnitudes [1–3]. For example, when instructed to attend to the physical size of a number while ignoring its numerical value, dyscalculic subjects, unlike healthy participants, fail to process the irrelevant dimension automatically and subsequently show a smaller size-congruity effect (difference in reaction time between incongruent [e.g., a physically large 2 and a physically small 4] and congruent [e.g., a physically small 2 and a physically large 4] conditions), and no facilitation (neutral [e.g., a physically small 2 and a physically large 2] versus congruent) [3]. Previous imaging studies determined the intraparietal sulcus (IPS) as a central area for numerical processing [4–11]. A few studies tried to identify the brain dysfunction underlying developmental dyscalculia but yielded mixed results regarding the involvement of the left [12] or the right [13] IPS. Here we applied fMRI-guided TMS neuronavigation to disrupt left- or right-IPS activation clusters in order to induce dyscalculic-like behavioral deficits in healthy volunteers. Automatic magnitude processing was impaired only during disruption of right-IPS activity. When using the identical paradigm with dyscalculic participants,

we reproduced a result pattern similar to that obtained with nondyscalculic volunteers during right-IPS disruption. These findings provide direct evidence for the functional role of right IPS in automatic magnitude processing.

Results

fMRI Data

Results for the whole-brain group and the behavioral data are presented in detail in the [Supplemental Data](#) available online. In line with previous studies [6, 8, 14], the size-congruity effect activated the bilateral intraparietal sulcus (IPS) (Figure 1). In order to accurately stimulate the functionally defined region of interest along the IPS for each participant in the transcranial magnetic stimulation (TMS) experiment, we analyzed the IPS size-congruity-effect activation for each individual separately. The results revealed considerable interindividual differences in the IPS activation both in extent and in layout and, therefore, in the stimulated coordinates (Figure 2, Table S1 in the Supplemental Data).

TMS Analysis

The mean reaction times (RTs) were subjected to a three-way analysis of variance (ANOVA) with TMS (left, right, or left/right sham), comparison (numerical or physical-size comparison), and congruency (incongruent, neutral, or congruent) as within-subject factors. The main effects for congruency (congruent, 447 ms; neutral, 471 ms; incongruent, 531 ms) [$F(2,8) = 13.96$, $p < 0.005$] and comparison (physical, 449 ms; numerical, 517 ms) [$F(1,4) = 62.07$, $p < 0.005$] were significant. The congruency effect was composed of a facilitatory component (congruent minus neutral) of 24 ms [$F(1,4) = 33.43$, $p < 0.005$] and an interference component (incongruent minus neutral) of 60 ms [$F(1,4) = 8.99$, $p < 0.05$]. Most importantly, the only factor interacting with TMS was congruency [$F(4,16) = 4.17$, $p < 0.05$] (Figure 3), and the triple interaction was not significant ($p > 0.9$). Additional analyses of the two-way interaction were conducted separately for each TMS stimulation site [15].

Sham IPS

The simple main effect of congruency was significant [$F(2,8) = 13.84$, $p < 0.005$]. Examination of the components of the congruency effect revealed a significant facilitatory component of 27 ms [$F(1,4) = 57.95$, $p < 0.005$] and a significant interference component of 63 ms [$F(1,4) = 8.05$, $p < 0.05$].

Left IPS

The simple main effect of congruency was significant [$F(2,8) = 11.53$, $p < 0.005$]. The effect was due to significant facilitatory [28 ms, $F(1,4) = 30.52$, $p < 0.005$] and interference components [78 ms, $F(1,4) = 8.11$, $p < 0.05$].

Right IPS

The simple main effect of congruency was significant [$F(2,8) = 11.72$, $p < 0.005$]. However, in contrast to results from the other TMS stimulation sites, this significance

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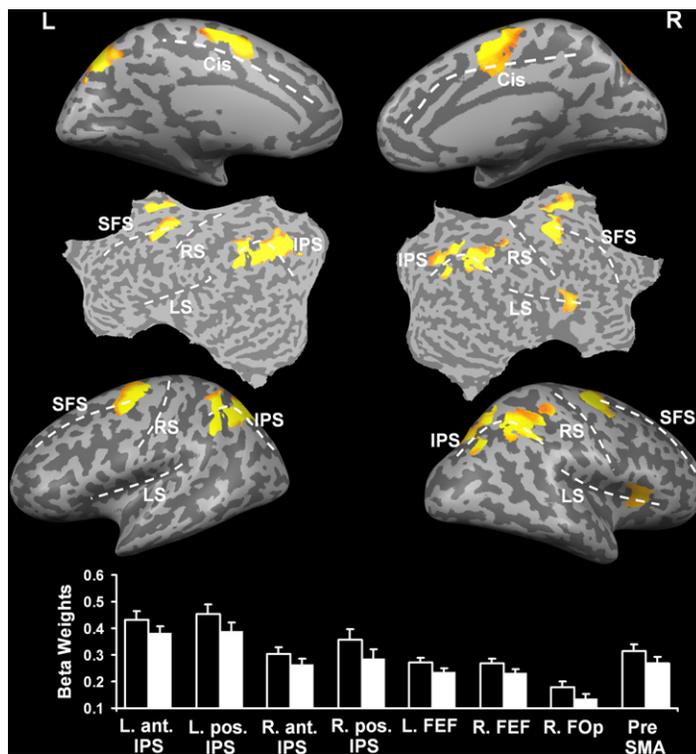


Figure 1. Size-Congruity Effect: Group Results

Multisubject ($n = 5$) general-linear-model surface map, superimposed on flattened (second row) and inflated (first row-medial view; third row-lateral view) representations of the cortical sheet of a template brain. The yellow-orange color represents foci that showed significant activations for the main effect of size congruity (incongruent greater than congruent). The bottom row-representation graph displays the beta weights for the different areas, as a function of congruity (incongruent in black, congruent in white). The following abbreviations are used: cingulate sulcus (Cis), intraparietal sulcus (IPS), frontal eye field (FEF), frontal operculum (Fop), lateral sulcus (LS), superior frontal gyrus (SFS), supplementary motor area (SMA), and rolandic sulcus (RS).

was mainly due to a significant interference component of 40 ms [$F(1,4) = 8.63$, $p < 0.05$], whereas the facilitatory component failed to reach significance [$F(1,4) = 6.68$, not significant (ns)]. Further analysis (Supplemental Data) ruled out that this lack of facilitation was due to faster RTs in the neutral condition [16] or neglect-like performance.

Error Rates

We found main effects of comparison [$F(1,4) = 8.61$, $p < 0.05$] and congruency [$F(1,4) = 9.97$, $p < 0.01$]. The pattern of the effects mirrored the RT effects and thus excluded any RT-accuracy trade-off influences.

Dyscalculic Group

The mean RTs were subjected to a two-way ANOVA with comparison and congruency as within-subject factors. The main effects of comparison (physical, 538 ms; numerical, 609 ms) [$F(1,4) = 10.87$, $p < 0.05$] and congruency [$F(2,8) = 12.72$, $p < 0.005$] were significant. Similar to that for healthy subjects during right-parietal TMS, the congruency effect in the dyscalculic group was composed of a significant interference component [$F(1,4) = 8.70$, $p < 0.05$] but no facilitation [$F(1,4) = 3.31$, ns] (Figure 3). The interaction between comparison and congruency was not significant [$F(2,8) = 1.73$, ns].

Discussion

The current results shed light on the essential role of the parietal lobes in automatic magnitude processing and offer a possible hemispherical locus for developmental dyscalculia. By combining functional magnetic resonance imaging (fMRI) and neuronavigated TMS, we demonstrated that although both intraparietal sulci are involved during automatic magnitude processing, only a neuronal disruption of the right IPS significantly

impairs automatic magnitude activation. To compare these findings with those of a clinical population, we examined participants suffering from developmental dyscalculia and were able to show that their performance mirrored the performance of healthy subjects receiving right-parietal TMS.

Our findings of bilateral IPS activation during fMRI, but only unilateral behavioral TMS effects, are in line with the idea of degenerate neuronal systems [17] (Supplemental Data). Our results thus indicate that the right, but not the left, IPS is functionally necessary for automatic magnitude processing. This right lateralization does not contradict previous findings that suggested a possible role for the left hemisphere in numerical processing [12]. Rather, we suggest that such findings might stem from inefficient processing of the verbal component of numbers (for a similar idea, see [18]).

Previous studies [19, 20] have pointed out the relationship between right-parietal-lobe dysfunction and visuospatial impairments in people with pure developmental dyscalculia (e.g., dyscalculia without other disorders, such as dyslexia). A large number of studies have documented the crucial role of the right IPS in visuospatial abilities [21–23]. Additionally, in the number domain, it has also been shown that a right-parietal lesion (or disruption by TMS) affects visuospatial processing, which in turn affects numerical processing [24–26]. In line with this evidence, Walsh [27] proposed “a theory of magnitude” (ATOM) and suggested that the right IPS is active for different types of magnitude, regarding space, time, and quantity. Interestingly, as predicted by ATOM, the impairment of automatic magnitude processing in both the nondyscalculic and the dyscalculic group was independent of whether the comparison task was performed on quantity (number comparison)

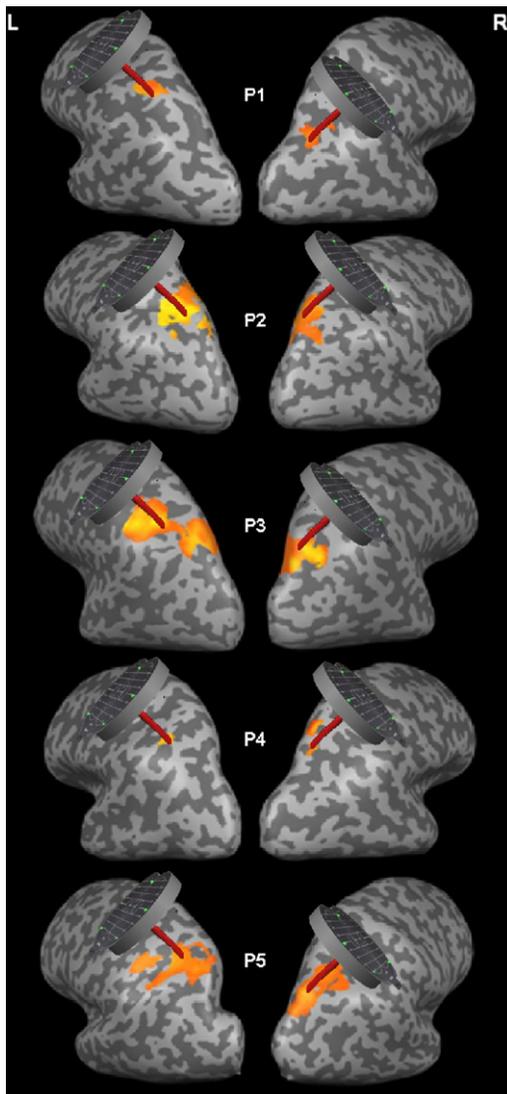


Figure 2. Size-Congruity Effect: Individual Results
The layout and the extent of the IPS activation as a function of the size-congruity effect in the left and right hemispheres for each individual participant. The tip of the red beam from the TMS figure-eight coil (shown from a lateral view) indicates the site of the maximal stimulation. P indicates the number of the participant.

or space (physical-size comparison). Hence, our results support the suggestion that the right IPS processes magnitudes such as numerical value or physical size, in general.

However, without simultaneously assessing the exact neural consequences of our focal TMS in the brain, we cannot rule out that we might have also modified neural activity in remote and interconnected brain regions [28–30]. Therefore, it might be more appropriate to interpret our findings as evidence that critical capacities required for automatic magnitude processing are affected by disruption of the right IPS and/or its connected neural network. Yet the possibility that connected brain areas outside the right parietal lobe have caused the current effect is unlikely because no brain area outside the parietal lobes shows systemic modulation due to general magnitude processing (e.g., [4–6, 8]).

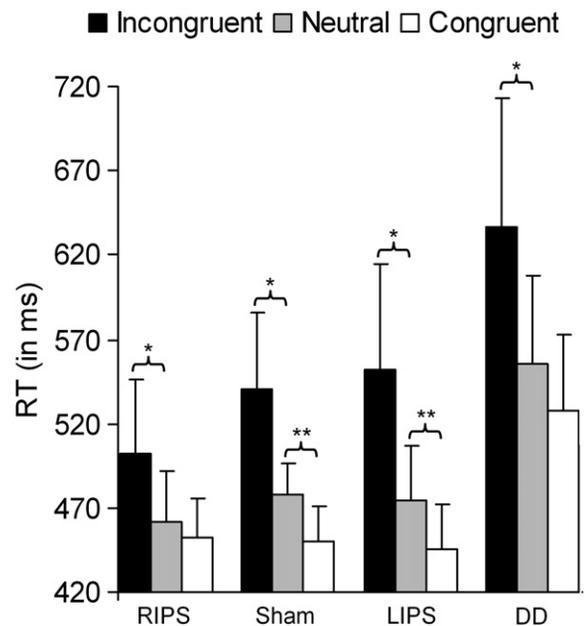


Figure 3. Reaction Times as a Function of Congruity for the Group with Developmental Dyscalculia and for TMS Stimulation Sites for the Nondyscalculic Group

Error bars depict one standard error of the mean. * < 0.05, ** < 0.005. The following abbreviations are used: developmental dyscalculia (DD), left IPS (LIPS), and right IPS (RIPS).

The IPS is a long, discontinuous sulcus [13] and shows a large intersubject variability both anatomically [31] and functionally [7]. This large intersubject variability can potentially result in suboptimal TMS positioning when individual fMRI data are ignored [32]. This might also account for the null results of previous TMS studies that used magnitude-comparison tasks, including the size-congruity paradigm [33]. In contrast, we used fMRI-based neuronavigation to position the TMS coil precisely above the site of the size-congruity effect in each individual participant and thus provided an accurate stimulation in each subject (Supplemental Data).

A word of caution is in order at this point. It remains unclear whether the TMS-induced transient-activity disruption and the neuronal mechanisms or pathophysiologies underlying the long-lasting deficits of developmental dyscalculia are identical. At the moment, we also cannot assess to what extent our findings are specific to the particular paradigm adopted in our study. Future studies are thus warranted in order to establish whether developmental dyscalculia is characterized by impairment of automatic magnitude processing in general or of numerical magnitudes in particular and to establish the generalizability of our findings.

Conclusions

The current findings reveal the functional necessity of the right parietal lobe for automatic activation of magnitude processing. Moreover, they demonstrate the capacity of neuronavigated right-parietal TMS to mimic the behavioral deficits characteristic of developmental dyscalculia. This form of virtual neuropsychology thus

allows us to experimentally investigate the possible neural substrates for dyscalculia in healthy participants. Our approach of directly comparing TMS-induced behavioral effects in healthy volunteers to the performance of participants suffering from developmental dyscalculia enables us to suggest a direct causal relationship between malfunctions along the right IPS and developmental dyscalculia. We hope that future studies will adopt the methodological framework offered here by using a variety of tasks for mapping the brain tissue involved in developmental dyscalculia and its possible subtypes.

Experimental Procedures

Overall Study Design

The nondyscalculic participants were tested in five separate sessions (Figure S1). In the first session, functional- and anatomical-MRI measurements were obtained (Supplemental Data). The data were used to provide the exact area along the IPS that exhibited the strongest size-congruity effect for each individual and to guide the TMS coil to the respective target locations (Supplemental Data). In the subsequent four TMS sessions, participants underwent event-related triple-pulse TMS while performing the size-congruity task. In order to compare the findings of the TMS experiment with a clinical population, we used the identical behavioral paradigm (only without the TMS stimulation) to test a group of participants suffering from developmental dyscalculia. The study was approved by the local ethics committee. All participants were recruited from an academic environment. Informed consent to participate was obtained from all participants.

Nondyscalculic Participants

There were five participants (four males, mean age = 28.6 years, standard deviation [SD] = 4.5), each with normal or corrected-to-normal vision and no history of neurological or psychiatric disorders. None of the participants had taken part in a TMS experiment before.

Dyscalculic Participants

The participants (five participants, three males, mean age = 27.2 years, SD = 4.8) in the current study were diagnosed via an age-standardized battery of arithmetic tests based on the neurocognitive model of arithmetic [34], which was composed by Shalev et al. [35] and was modified (for detailed information on the assessment of these participants, see [3]). No other developmental learning disabilities, such as dyslexia, dysgraphia, or attention deficit/hyperactivity disorder, were ever diagnosed in any of the participants.

Stimuli and Paradigm

In the size-congruity paradigm, a stimulus representing two dimensions is presented, and participants are instructed to attend to one dimension while ignoring the other. Behavioral studies have shown that healthy participants unintentionally process the irrelevant dimension [6, 10, 16, 36–39]. The stimuli consisted of two digits (vertical visual angle of 0.8° or 1.1°) appearing at the center of a screen. The center-to-center distance between the two digits subtended a horizontal visual angle of 4°. Numerical and physical-size comparisons were performed in separate blocks with congruent, neutral or incongruent pairs. In the congruent condition, one of the two digits is larger in both dimensions (e.g., a physically small 2 and a physically large 4). In the incongruent condition, one digit is larger in the task-relevant dimension and the other digit is larger in the task-irrelevant dimension (e.g., a physically large 2 and a physically small 4). In the neutral condition there is no difference in the irrelevant dimension (e.g., a physically small 2 and a physically small 4 for numerical comparison and a physically small 2 and a physically large 2 for physical-size comparison). Facilitation is observed when the response to congruent trials is faster than to neutral trials. Interference takes place when the response to incongruent trials is slower than to neutral trials.

Procedure

Participants were instructed to decide which one of two stimuli in a given display was numerically (numerical comparison) or physically (physical-size comparison) larger (Figure S2). They had to indicate their choice by pressing one of two keys corresponding to the side of the display, with a right hand response if the selected digit was on the right or a left hand response if it was on the left. Participants were encouraged to respond as quickly as possible while avoiding mistakes and to attend only to the relevant dimension in each task.

We used Presentation (Neurobehavioral Systems, San Francisco, CA) as stimulus-presentation software. The experiment was preceded by a training session.

TMS Experiment

Each nondyscalculic volunteer underwent four TMS sessions spread over two different days. The order of numerical and physical blocks was counterbalanced in an ABBA design for three participants and in a BAAB design for the rest. The order of real and sham stimulation to the left IPS and right IPS (four sessions) was also counterbalanced. On each day, two sessions took place. Per day, participants received real TMS to one hemisphere and sham TMS to the other hemisphere. The stimulation order for the fifth participant was randomly chosen. Congruent, neutral, and incongruent conditions were randomly sampled, and there was an equal sampling for each condition. A total of 576 trials were presented to each participant (24 trials × 4 sessions [right TMS, left TMS, right sham, left sham] × 3 congruencies [incongruent, neutral, and congruent] × 2 tasks [physical/numerical]). Correct responses had to be made equally often with the left and right hand.

Each trial began with an asterisk as a fixation point, presented for 500 ms at the center of a computer screen. Five hundred ms after the fixation point disappeared, a pair of digits appeared for 1 s. The intertrial interval was 6 s, and the interblock interval was at least 15 s.

Behavioral Data Analysis

Mean RTs for every participant in each condition were calculated for correct trials only. RTs that were 2.5 standard deviations from the mean of each condition for each individual were excluded (less than 2%).

Supplemental Data

Supplemental Data include Supplemental Results, Supplemental Discussion, Supplemental Experimental Procedures, one table, and six figures and are available online at <http://www.current-biology.com/cgi/content/full/17/8/689/DC1/>.

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