TMS over the left angular gyrus impairs the ability to discriminate left from right

Marco Hirnstein*, Ulrike Bayer, Amanda Ellison, Markus Hausmann

Department of Psychology, University of Durham, United Kingdom

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ABSTRACT
The underlying cognitive and neural mechanisms of the ability to discriminate left from right are hardly explored. Clinical studies from patients with impairments of left–right discrimination (LRD) and neuroimaging data suggest that the left angular gyrus is particularly involved in LRD. Moreover, it is argued that the often reported sex difference in LRD, with women being more susceptible to left–right errors than men, is the result of a stronger lateralization in men than women. Offline repetitive transcranial magnetic stimulation (rTMS) was used to test whether the left angular gyrus is involved in LRD and whether men have a stronger lateralization in LRD than women. Twenty-four participants (12 men, 12 women) completed a behavioral LRD task in three different conditions: after rTMS of the left and right angular gyrus and after ‘sham’ rTMS (control). The results revealed that after rTMS of the left angular gyrus, LRD accuracy rates were significantly reduced compared to the control condition. After rTMS of the right angular gyrus no difference to the control condition was observed. In addition, there was no overall sex difference in the LRD task and men and women were similarly affected by stimulation over the left and right angular gyrus, suggesting that the functional cerebral organization of LRD does not differ in men and women with similar LRD skills. Taken together, the findings suggest that the left angular gyrus is critically involved in LRD. It is argued that the left angular gyrus integrates spatial information with the meaning of the words ‘left’ and ‘right’, thereby assigning the labels ‘left’ and ‘right’ to a certain state or direction, etc.

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1. Introduction

Every day humans are faced with left–right decisions making the ability to discriminate left from right a useful and sometimes crucial skill. Although we are generally accurate when making left–right decisions, mixing up left with right remains a ubiquitous phenomenon. However, little is known about the underlying cognitive processes and even less about the neural mechanisms that enable us or hinder our ability to discriminate left from right.

Evidence from clinical studies suggests that the left angular gyrus (ANG) is particularly involved in left–right discrimination (LRD). For example, difficulties with LRD have been described in patients suffering from Gerstmann’s syndrome, a neurological disorder that comprises acalculia, agraphia and finger agnosia (Gerstmann, 1924). It remains unclear, however, whether Gerstmann’s syndrome is a distinct neurological disorder or a cluster of distinct deficits. The literature rather suggests the latter, arguing that these deficits are likely to co-occur because the underlying processes are all localized around the intraparietal sulcus and supplied by the angular gyrus artery (Dehaene, Piazza, Pinel, & Cohen, 2003). Regardless of whether Gerstmann’s syndrome is a distinct disorder or not, the symptoms including left–right confusion typically occur after lesions of the ANG and supramarginal gyrus, particularly in the left hemisphere (Gold, Adair, Jacobs, & Heilman, 1995). Rusconi, Walsh, and Butterworth (2005) were able to induce impairments in number and finger processing, two of the four deficits in Gerstmann’s syndrome, by stimulating the ANG with repetitive transcranial magnetic stimulation (rTMS). While they did not explore LRD, it thus seems reasonable to assume that rTMS over the ANG and particularly over the left ANG also impairs the ability to discriminate left from right.

In addition to evidence from patients with neurological deficits only a couple of neuroimaging studies investigated the brain areas involved in LRD in neurologically healthy participants. A regional cerebral blood flow study (Hannay, Leli, Falgout, Katholi, & Halsey, 1983) reported bilateral activations of the occipital lobe and a left-hemispheric activation of the parietal lobe. The activation of the left parietal lobe is thus in alignment with clinical studies suggesting that the left ANG is involved in LRD. The bilateral occipital activation might result from the fact that a visual LRD task was
used. Interestingly, while there was no sex difference in the activation pattern, men’s performance in the LRD task was negatively correlated with the regional cerebral blood flow in these cortical areas. No such correlation was observed in women, suggesting that correlation with the regional cerebral blood flow in these cortical areas is necessary for LRD, that is, whether a lesion or temporary impairment of these areas leads to deterioration in LRD. The present study therefore uses rTMS to investigate the role of the left and right ANG in LRD. It was hypothesized that only rTMS over the left ANG would lead to a temporary impairment of the ability to make left–right decisions.

A further goal of the present study was to explore the origins of individual differences in LRD. Some people seem to be more susceptible to mixing up left with right than others. For instance, a number of studies have demonstrated that women have more difficulty with LRD than men (Bakan & Putnam, 1974; Hirnstein, Okkenburg, Schneider & Hausmann, 2009; Otte, 2002; Otte & Hugdahl, 2002a; Snyder, 1991; Vingerhoets, Lannoo, Bauwens, 1996; but see Jordan, Wüstenberg, Jaspers-Feyer, Fellbrich & Peters, 2006; Williams, Standen & Ricciardelli, 1993). This sex difference in LRD has been associated with sex differences in hemispheric asymmetry. It was argued (e.g. Bakan & Putnam, 1974) that men have less difficulty with LRD than women, because LRD is enhanced by hemispheric asymmetry (Corballis & Beale, 1970; Corballis & Beale, 1976) and men are assumed to possess a more asymmetrical brain than women (e.g. Hiscock, Inch, Jacek, Hiscockkalil, & Kalil, 1994; Hiscock, Israelian, Inch, Jacek, & Hiscockkalil, 1995, but see Sommer, Aleman, Bouma, & Kahn, 2004; Sommer, Aleman, Somers, Boks, & Kahn, 2008; Boles, 2005). Indeed, there is some evidence that hemispheric asymmetry might be associated directly with sex differences in LRD. Hirnstein et al. (2009) demonstrated that in participants with a clear language lateralization, measured with a fused rhymed words dichotic listening test, men have less difficulty with LRD than women, whereas the sex differences emerged in participants who do not show a clear language lateralization. We therefore also intended to investigate whether the sex difference in LRD directly depends upon the degree of functional lateralization in LRD. If men have on average functionally more lateralized brains in LRD than women, it is hypothesized that (a) men would be more affected by rTMS over the left ANG than over the right ANG and (b) women would be less susceptible to rTMS over either ANG than men because a stronger bilateral brain organization in men might compensate unilateral functional disruptions more efficiently than does the rather asymmetric brain organization in women. The rationale is similar to Knecht et al. (2002) who stimulated language regions in the left and right hemisphere of less and strongly lateralized participants. They found that in comparison to strongly lateralized participants less lateralized participants were hardly affected by rTMS over either hemisphere.

Taken together, evidence from clinical and neuroimaging studies suggest that particularly the left ANG plays a crucial role in LRD. This effect might be particularly pronounced in men compared to women who are expected to be less susceptible to rTMS because of a rather bilateral functional brain organization in LRD. By employing the offline variant of the TMS technique we could investigate the left and right ANG in an environmentally valid yet cognitively taxing task which requires processing times too long for conventional event related TMS.

2. Methods
2.1. Participants

Twenty-four healthy participants (12 women, 12 men) took part in the present study. The mean age for women was 31.1 (SD = 8.8) years and 29.3 (SD = 11.4) years for men. The sample size was based on a power analysis to have sufficient power (80%, α-level = 5%) to detect sex differences. The estimated effect size of $\eta^2 = 0.15$ based on previous studies (Hirnstein et al., 2009; Otte, 2002) suggests a minimum required sample size of $N = 24$. All participants were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). The laterality quotient (LQ) provided by this test is calculated as $\text{LQ} = ((R - L)/(R + L)) \times 100$, resulting in values between $-100$ and $+100$. Positive values indicate a preference for the right hand, negative values a left-hand preference. Women had a mean LQ of 91.33 (SD = 12.34), men a mean LQ of 89.82 (SD = 9.78). Participants gave their signed informed consent in accordance with the Declaration of Helsinki and with the approval of Durham University Ethics Advisory Committee, and could leave the experiment at any time. All participants were checked for EMS exclusion criteria (Wassermann, 1998).

2.2. Task and procedure

A modified version of the Bergen Left–Right Discrimination Test (Otte, 2002; Otte & Hugdahl, 2002a; Otte & Hugdahl, 2002b) was employed. Participants were presented pictures of human stickman figures, whose left or right hand were highlighted in red (Fig. 1). The stickman figures were either depicted in a way that they faced the participant (front view), or in a way that they looked away from the participant (back view, indicated by a filled black circle). Below each stickman figure was a label showing either ‘left’ or ‘right’, which referred to the highlighted hand. Participants were asked to indicate via button press whether the label was correct or not. For example, if the label ‘left’ corresponded to the highlighted hand of the stickman figure this was a correct trial. If the label did not correspond to the highlighted hand, this was an incorrect trial. To avoid stimulus/response compatibility effects, response buttons were in an up/down arrangement: the ‘2’ and ‘8’ key of a standard keyboard number pad denoted ‘incorrect’ and ‘correct’, respectively. Participants were instructed to answer as accurately and as quickly as possible.

Participants sat with their eyes 57 cm away from a CRT computer monitor on which the stickman figures were presented. Their head was placed on a chin rest to minimize head movements. Each trial began with the presentation of a stickman figure and the stickman figure remained on the screen until participants’ response. The next trial began with an inter-stimulus interval of 1 s. In total, 48 trials were presented, half of them required a ‘correct’ and half of them required an ‘incorrect’ response. Also, in half of the trials stickman figures were shown from the front and in half of the trials from behind. Half of the participants used their left, half of the participants used their right hand to respond. Overall, participants completed three experimental blocks: one block after offline stimulation of the left ANG, one block after offline stimulation of the right ANG and one block after ‘sham’ stimulation. In the ‘sham’ stimulation, which served as a control condition, the coil was placed on the head opposite to the participant, while an additional coil with no magnetic pulses was held against the participant’s skull. The position of the dummy coil was central between the left and right ANG along the median plane, so that the distance between the left ANG and control site was identical to the distance between the
right ANG and control site. The block order was counterbalanced. Prior to the experiment, participants completed at least eight practice trials until they felt confident about following task instructions. Each experimental block started with a further four practice trials. Accuracy rates and median reaction times of correct responses were recorded.

2.3. Magnetic stimulation

The left and right ANG of all participants were located on the basis of structural brain images by using frameless stereotaxy. The position of the participant’s head was tracked with a Polaris™ (Northern Digital, Waterloo, Ontario, Canada) infrared tracking device and the co-registration of the participant’s head and her/his anatomical scan was accomplished withBrainsight™ software (Rogue Research, Montreal, Canada).

Offline rTMS with a stimulation frequency of 1 Hz was performed using a 70 mm diameter figure-of-eight coil connected to a Magstim™ Super Rapid magnetic stimulator (The Magstim Co. Ltd., Whitland, UK). During rTMS, the center of the coil was held tangentially on the skull over the ANG in a constant position with the handle pointing medially parallel to the horizontal and midsagittal plane. The stimulation intensity was set at 60% of stimulator output (approx 1.1 Tesla) with one pulse applied per second for 10 min (600 pulses). According to the literature, this procedure should affect the neural activity of the ANG for approximately 6 min (Udden et al., 2008; Walsh & Pascual-Leone, 2003). Directly after rTMS (or sham-stimulation), participants completed one block of the modified Bergen Left–Right task for approximately 5 min. Subsequently, there was a 20–30-min break before the next block so that neural activity returned to baseline.

3. Results

Throughout, effect sizes are provided as the proportion of variance accounted for (partial $r^2$) and $p$-levels for post hoc $t$-tests were adjusted using Bonferroni correction.

A $3 \times 2 \times 2$ ANOVA with the within-participants factors TMS-stimulation (left ANG, right ANG, control) and stickman figure view (back view, front view) and the between-participants factor sex was computed for accuracy rates and reaction times (see Table 1). For accuracy rates, a significant main effect TMS-stimulation was found ($F(2, 44) = 4.57, p = .016, r^2 = 17.2$). Posthoc $t$-tests revealed that the accuracy rate was significantly reduced after stimulation of the left ANG ($t(23) = 2.73, p = .037$, see Fig. 2) but not after stimulation of the right ANG ($t(23) = 1.76, ns$) compared to the control condition.

When comparing the two experimental conditions (stimulation of the left and right ANG), a one-tailed $t$-test only approached significance ($t(23) = 1.50, ns$). Moreover, there was a significant main effect stickman figure view ($F(1, 22) = 4.56, p = .044, r^2 = 17.2$), indicating lower accuracies for trials showing stickmen figures in the front view ($M = 89.58\% \pm SE = 1.25$) than in the back view ($92.77\% \pm 71$). Although men were numerically more accurate, there was no significant main effect sex ($F(1, 22) = 1.89, r^2 = 8.9, ns$) and no further interaction became significant (all $F \leq 2.30, ns$). In reaction times, the main effect stickman figure view was significant ($F(1, 22) = 23.10, p < .001, r^2 = 51.2$). Participants responded more slowly to stickmen viewed from the front ($2701 \text{ ms} \pm 174$) than from the back ($2400 \text{ ms} \pm 173$). The main effect sex was not significant ($F(1, 22) = 0.15, r^2 = 0.1, ns$). As such, there were no further main effects or interactions (all $F \leq 1.55, ns$).

4. Discussion

The present study revealed that stimulation of the left ANG with offline rTMS leads to a transient impairment of the ability to make left–right decisions. This is in accordance with (a) studies on patients with lesions of the left ANG who have difficulties with LRD (Ardila, Concha, & Rosselli, 2000; Gold et al., 1995) and (b) a functional imaging study that found activations in the left parietal lobe during a behavioral LRD task in neurologically healthy participants (Hannay et al., 1983). The impairment in LRD after stimulation of the left ANG manifested relative to the control condition. There was only a trend in the direct comparison between left and right ANG. The mean accuracy rates suggest that stimulation over the right ANG led to a minor reduction in LRD which may have been enough to abolish a significant difference between left and right ANG, but was too weak to become significant with respect to the control condition. Thus, the right ANG may also be involved in LRD. However, only stimulation over the left ANG has noticeable, behavioral effects on LRD.

Although an involvement of the left ANG in LRD has been suggested before, its exact role is still unclear. We propose that left–right errors are predominately the result of assigning the wrong verbal label to a certain direction or object (e.g. labeling the right hand as ‘left’) and that the left ANG is particularly involved in assigning these verbal labels. In principle, left–right decisions require two vital steps (Farrell, 1979). The first step is a perceptual or spatial encoding process. In the present experiment, for example, participants first have to encode on which side of the body the highlighted hand is located. The second step is to label that side with the word ‘left’ or ‘right’. The literature supports the idea that left–right errors are typically the result of assigning a wrong label and not incorrect perceptual or spatial encoding. In a series of experiments, for example, Sholl and Egeth (1981) dismantled the perceptual/spatial encoding process from the verbal labeling process and concluded that “…our results support a verbal labeling explanation for left–right confusion in the adult” (Sholl & Egeth, 1981, p. 339; see also Maki, Grandy, & Hauge, 1979). There is reason to believe that the left ANG plays a vital part in assigning verbal labels to directions and objects. The left ANG is involved in a number of language-related processes. Specifically, it

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**Table 1**

Mean accuracy rates in % (SD in brackets) across men, women and all participants after stimulation of the left and right ANG and sham stimulation (control) for back and front view stickman figures.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Back view</th>
<th>Front view</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (sham)</td>
<td>94.10 (3.30)</td>
<td>93.40 (6.99)</td>
</tr>
<tr>
<td>Left ANG</td>
<td>91.67 (3.97)</td>
<td>90.28 (8.21)</td>
</tr>
<tr>
<td>Right ANG</td>
<td>92.01 (7.42)</td>
<td>91.32 (8.42)</td>
</tr>
<tr>
<td>Men</td>
<td>94.10 (3.30)</td>
<td>93.40 (6.99)</td>
</tr>
<tr>
<td>Women</td>
<td>94.79 (3.61)</td>
<td>91.32 (10.58)</td>
</tr>
<tr>
<td>All</td>
<td>94.44 (3.40)</td>
<td>92.36 (8.83)</td>
</tr>
</tbody>
</table>

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**Fig. 2.** Mean accuracy rates (with SE) across the left ANG, right ANG and control condition.
is important for semantic processing of language and assessing the meaning of words (Price, 1998). Also, the ANG is part of the inferior parietal lobe and adjacent to the intraparietal sulcus. Both areas are involved in spatial processing (e.g. Grefkes & Fink, 2005, for review). It thus seems reasonable to assume that the left ANG integrates spatial information that is necessary for making left–right decisions with the meaning of the words ‘left’ and ‘right’, thereby assigning the labels ‘left’ and ‘right’ to a certain state or direction, etc. A transient stimulation of the left ANG using offline rTMS as in the present study could have thus led to an impairment of this integration process and consequently resulted in a lower accuracy rate.

While most studies suggest that the left ANG is critical for left–right decisions, there is also evidence for an involvement of the right hemisphere. For example, a recent fMRI study reported stronger activations in the right hemisphere during LRD (Auer et al., 2008). Here, participants were asked to show numbers with the fingers of either their left or right hand following verbal commands. Moreover, split-brain patients showed a right-hemisphere advantage when they had to discriminate mirror images, that is, indicating whether a letter is presented normally or in backward orientation, for example (Corballis, Birse, Paggi, Manzoni, & Fabri, 2010; Corballis & Sergent, 1989; Funnell, Corballis, & Gazzaniga, 1999). However, mirror image discrimination can be performed without assigning the words ‘left’ or ‘right’ and thus without verbal labeling. Moreover, mirror image discrimination involves mental rotation, which, in general, has been considered to be lateralized to the right hemisphere (Corballis, 1997). In fact, many LRD studies require participants to mentally rotate two or three-dimensional objects. It is therefore likely that the two critical processes for LRD, spatial/perceptual encoding and verbal labeling, are provided by the two hemispheres. That is, the spatial/perceptual encoding process, which comprises, for example, mental rotation, is predominantly carried out by the right hemisphere and the verbal labeling process by the left. The conflicting results regarding which hemisphere is predominantly involved in LRD could then be explained by different LRD task demands. If verbal labeling is critical for an LRD task, a left-hemispheric advantage should emerge, whereas a right-hemispheric advantage should emerge, if mainly spatial/perceptual encoding is required.

The present study aimed to disentangle mental rotation and LRD by presenting front and back views of the stickman figures. The back views do not involve mental rotation as the participants’ left is the stickman’s left but the front view pictures require either rotating the figure or oneself with respect to the figure to identify the figure’s left. As expected, front view pictures were generally more difficult than back view pictures. If mental rotation is lateralized to the right hemisphere, one could have expected stronger impairments for front view pictures following stimulation of the right ANG (in contrast to the left ANG). Yet, rTMS of only the left ANG seem to affect both front and back view pictures. It is possible that stimulation of the right ANG is simply too focal to find mental rotation effects as it is only a part of a larger cortical network devoted to mental rotation (Zacks, 2008). However, this finding may further suggest that spatial/perceptual processes were not as relevant as verbal labeling processes in the LRD task of the present study.

Our stimulation paradigm ensured that neural firing in the region of interest occurs at a lower rate throughout the processing of the task. One disadvantage of this is that the temporal specificity of a region cannot be defined. However, this cannot explain the lack of effect in the right ANG. This dissociation suggests that there is no spread of functional effect between ANGs following unilateral rTMS even though it is now well accepted that there is a concurrent electrical activation in the contralateral hemisphere (see Komssi & Kähkönen, 2006 for review), which might also explain the numerical decrease in LRD performance following right ANG stimulation. However, there is no evidence that contralateral electrical activation can cause a functional impairment as seen with ipsilateral stimulation. The TMS effects on performance manifested as a decrease in accuracy. However, as it is common in TMS experiments, performance is not abolished, but merely interfered with due to the introduction of noise in an area whose efficient processing is required for accurate processing of the task (Ellison, Batelli, Cowey, & Walsh, 2003; Ellison & Cowey, 2009). It may be however that the impaired processing of the left ANG was slightly bolstered by compensatory activity in the right ANG. Also, it could be that the left ANG is a part of a larger neural network devoted to LRD that can compensate for a loss or impairment of one of its components. This network explanation is in accordance with the aforementioned study of Auer et al. (2008) that reported activations in frontal, temporal and parietal areas during LRD. Due to the paucity of studies on the neural basis of LRD, it is too early to decide which of these explanations, if any, accounts for the relatively preserved LRD performance after TMS of the left ANG. Possibly, a combination of a merely reduced functional capability of the left ANG and a larger network might explain our findings.

The second aim of the present study was to investigate whether the often reported sex difference in LRD is the result of a stronger lateralization in men than in women. In contrast to the literature (Bakan & Putnam, 1974; Hirnstein et al., 2009; Ofte, 2002; Ofte & Hugdahl, 2002a; Snyder, 1991; Vingerhoets et al., 1996) we did not find that men were more accurate or faster in LRD than women. It is possible that practice effects have masked the sex difference in the LRD task of the present study as participants had to complete it three times. Moreover, since effect sizes for our LRD task could only be roughly estimated from previous studies (Hirnstein et al., 2009; Ofte, 2002), the minimum sample size of N = 24 may be too small to detect sex differences. However, as men and women were similarly susceptible to mixing up left with right, it is not surprising that they were also similarly affected by rTMS. Both men and women showed impaired LRD after simulation of the left ANG, suggesting that if there are no sex differences in LRD skills there are also no sex differences in the functional cerebral organization of LRD. It is, however, still possible that the higher susceptibility to left–right confusion in women that was reported previously emerged from potential sex differences in lateralization.

A potential problem of the present study may be factors that are confounded with the LRD task. Participants, for example, had to code that a black circle corresponds to the back of the stickman’s head whereas an empty circle corresponds to the participants face. While a number of clinical and neuroimaging studies suggest an involvement of the left ANG in LRD it cannot be entirely ruled out that these additional operations were disrupted by stimulating the left ANG. As a result, the performance in this task could have been reduced. Ratcliff (1979) used a similar LRD task with more realistic stickman figure’s whose back and front was easier to identify. Employing these stimuli in future studies would facilitate the coding and reduce the potential risk of confounding effects. Taken together, the present study suggests that the left ANG is involved in the integration of spatial left–right information and corresponding verbal labels. Consequently, impairments or lesions of the left ANG result in impairments or losses of the ability to discriminate left from right, especially when verbal labeling is required in LRD. Moreover, the present study did not find sex differences in LRD or sex differences with respect to the functional lateralization of LRD, suggesting that if men and women have similar LRD skills, they also show a similar functional cerebral organization of LRD.

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