

The neural correlates of sex differences in left-right confusion

Helene Hjelmervik¹, René Westerhausen^{1,2}, Marco Hirnstein¹, Karsten Specht^{1,3}, Markus Hausmann⁴

1 Department of Biological and Medical Psychology, University of Bergen, Bergen, Norway

2 Department of Psychology, University of Oslo, Oslo, Norway.

3 Department of Clinical Engineering, Haukeland University Hospital, Bergen, Norway

4 Department of Psychology, Durham University, Durham, United Kingdom

Corresponding author

Helene Hjelmervik

Department of Biological and Medical Psychology, University of Bergen

Jonas Lies Vei 91, 5009 Bergen, Norway

Telephone: +47-55-586221

Fax: +47-55-589872

Email: Helene.Hjelmervik@psybp.uib.no

Abstract

Difficulties in left-right discrimination (LRD) are commonly experienced in everyday life situations. Here we investigate the neurocognitive mechanisms of LRD and the specific role of left angular gyrus. Given that previous behavioral research reported women to be more susceptible to left-right confusion, the current study focuses particularly on the neural basis of sex differences in LRD while controlling for potential menstrual cycle effects (repeated measures design). 16 women and 15 men were presented pictures of pointing hands in various orientations (rotated versus non-rotated) and were asked to identify them as left or right hands. Results revealed that LRD was particularly associated with activation in inferior parietal regions, extending into the right angular gyrus. Irrespective of menstrual cycle phase, women, relative to men, recruited more prefrontal areas, suggesting higher top-down control in LRD. For the subset of rotated stimuli as compared to the non-rotated, we found leftward asymmetry for both men and women, although women scored significantly lower. We conclude that there are sex differences in the neurocognitive mechanisms underlying LRD. Although the angular gyrus is involved in LRD, several other parietal areas are at least as critical. Moreover, the hypothesis that more left-right confusion is due to more bilateral activation (in women) can be rejected.

Keywords: Left-right discrimination, sex differences, hemispheric asymmetry, menstrual cycle, fMRI.

1. Introduction

Left-right discrimination (LRD) refers to the ability to distinguish left from right, and many people struggle with this in their everyday life. The complexity of LRD, as compared to other locative labels (e.g., up/down, front/back) arises from the relative nature of left and right that changes with the position of a person. One can thus distinguish between LRD made from one's own perspective (i.e., egocentric) or someone else's perspective (i.e., extra-egocentric). The latter is believed to be more demanding, as one has to mentally rotate the object/person to match it onto one's own left/right perspective before LRD is done. Although left-right confusion is a widely experienced phenomenon, its underlying neurocognitive mechanisms still remain unknown.

Our understanding of the neurocognitive process behind LRD was to a large extent derived from studies of patients with Gerstmann syndrome. The Gerstmann syndrome is a condition involving symptoms of left-right confusion in addition to finger agnosia, agraphia, and acalculia, along with absence of any obvious disability in overall visuospatial processing (Gerstmann, 1957). Gerstmann (1957) described the underlying issue of Gerstmann syndrome as degraded body schema that leads to distortion of LRD. However, subsequent studies have suggested other causes of left-right confusion. Some researchers find that left-right confusion is mainly a visuospatial perception problem, due to difficulties in deriving the relative position of objects along the horizontal axis only (Gold et al., 1995). Others again describe left-right confusion as a verbal labeling problem (Sholl and Egeth, 1981), suggesting that application of the verbal labels ("left" and "right") to judgments of relative locations causes the confusion. Thus, LRD is thought to be dependent on multiple cognitive operations (i.e., visual, linguistic, and body

representations), and the underlying causes of left-right confusion in patients and healthy subjects are still a matter of debate.

Independently of the underlying cause, Gerstmann syndrome is usually found in patients with lesions (or other pathologies) to the angular gyrus in the transition zone to the occipital lobe of the left hemisphere (Gerstmann, 1957; Gold et al., 1995; Mayer et al., 1999). However, as reviewed by Arbuse (1947), many clinical cases also suggest lesions in the supramarginal gyrus and more rarely the postcentral gyrus. A cortical stimulation case-study revealed the posterior portion of the left temporoparietal junction is critical for LRD (Morris et al., 1984). This might suggest a larger anatomical basis for LRD, or individual differences of involved cortical areas. The few neuroimaging studies on LRD conducted on healthy participants mostly confirm the findings from previous lesion studies. Two rather old imaging studies found bilateral occipital (Hannay et al., 1983; Leli et al., 1982), as well as bilateral parietal (Leli et al., 1982), and the left parietal (Hannay et al., 1983) increase in blood flow during LRD. The particular involvement of the left hemisphere is further supported by a more recent transcranial magnetic stimulation (TMS) study (Hirnstein et al., 2011), which showed that repetitive TMS (1 Hz) over the left angular gyrus disrupts LRD, as compared to TMS over the right angular gyrus. The only fMRI study conducted on LRD so far, however, contradicts the assumption of left hemispheric dominance as a stronger right-hemispheric activation was found, including angular gyrus (Auer et al., 2008). As the study used only egocentric stimuli, the researchers speculated that there might be a left-hemispheric dominance for extra-egocentric stimuli. However, this was never tested. The study furthermore did not conduct a direct comparison of the BOLD response of the two hemispheres (Liegeois et al., 2002; Westerhausen et al., 2014).

However, the exact role of angular gyrus in LRD is not known. Hirnstein et al. (2011) highlights the left angular gyrus' role in semantical processing of verbal stimuli, and speculate that this is the region where spatial information is integrated with the meaning of the words left and right. Similarly, Seghier (2013) pinpoint the angular gyrus as a cross-modal hub where converging information of different modalities and subsystems are combined for manipulation of mental representations. This interpretation is appealing considering the multiple visuospatial, verbal, and somatic processes underlying LRD. It is also worth mentioning that the right angular gyrus has been proposed crucial in own-body perceptions (Blanke et al., 2002) which might be a prerequisite for locating one's own left and right side.

Research has consistently revealed more left-right confusion in women in everyday life than in men (Hannay et al., 1990; Hirnstein et al., 2011; Hirnstein et al., 2009; Williams et al., 1993; Wolf, 1973). When tested experimentally, some studies has confirmed this sex difference as women perform less accurately on LRD tasks as compared to men (Ocklenburg et al., 2011; Ofte and Hugdahl, 2002; but also see Hirnstein 2011, Jordan et al. 2006). Only one rather old imaging study has looked at the underlying neuro-cognitive mechanism for sex differences in left-right confusion. However, no differences between men and women were found (Hannay et al., 1983). In this study, the spatial resolution of the applied imaging method was too low to investigate detailed anatomical involvement in men and women, which might partly explain the lack of a sex difference finding in brain activation. Nevertheless, men's performance in the LRD task Hannay et al. applied, was negatively correlated with the regional cerebral blood flow in the bilaterally activated occipital and left parietal cortical regions. No such correlation was observed in women, suggesting that men and women might rely on different neurocognitive processes in

LRD. It is important to note that in related visuospatial tasks, such as mental rotation, which has more frequently been studied with neuroimaging techniques, men have also been found to rely more on parietal (Thomsen et al., 2000; Weiss et al., 2003) regions. In contrast, women typically engage prefrontal (mostly left) regions in a higher degree than men (Butler et al., 2006; Hugdahl et al., 2006; Thomsen et al., 2000; Weiss et al., 2003), and this is suggested to reflect different cognitive strategies. Sex differences in LRD might therefore be grounded in poorer visuospatial bottom-up processing.

Sex differences in LRD might also be due to frequently reported sex differences in functional cerebral asymmetries. For example, it has been suggested (e.g. Bakan and Putnam, 1974) that the generally more bilateral brain organization sometimes found in women (Hiscock et al., 1995; Shaywitz et al., 1995; but see Sommer et al., 2004; Voyer, 1996) might make them more susceptible to left-right confusion than men. This assumption is based on early theories that only an asymmetric brain can distinguish left from right (Corballis and Beale, 1976), as the asymmetry would induce an internal bias between the left and the right side (Corballis and Beale, 1976; Vingerhoets and Sarrechia, 2009). In support of this idea, two previous studies have found that a higher degree of handedness and asymmetry in tactile sensitivity (Vingerhoets and Sarrechia, 2009), and visual asymmetry (Manga and Ballesteros, 1987) has been associated with less left-right confusion.

In spite of pronounced sex differences frequently reported for LRD, no study so far has controlled for the effect of fluctuating sex hormones on LRD. This might be important given that fluctuations in estradiol and progesterone levels have been shown to dynamically change functional cerebral asymmetries and interhemispheric interaction across the menstrual cycle in

both verbal (Bayer and Erdmann, 2008; Hausmann and Güntürkün, 2000; Sanders and Wenmoth, 1998) and visuospatial tasks (Hausmann, 2005; Hausmann et al., 2002; Hausmann and Güntürkün, 2000; Hausmann et al., 2013). Furthermore, spatial abilities such as mental rotation has been found to fluctuate across the menstrual cycle, showing lower performance in the luteal phase during high levels of estradiol and progesterone (Hausmann et al., 2000; McCormick and Teillon, 2001; Schoning et al., 2007; but see Liben et al., 2002).

The primary purpose of the current fMRI study was to investigate the neural basis of LRD in general, and of sex differences in particular. The latter was achieved by taking into account women's sex hormonal state during different phases of the menstrual cycle. Only one fMRI study on LRD has previously been conducted, in men only (Auer et al., 2008). However, this study argues against the notion of the dominant left hemispheric contribution in LRD as previously suggested by lesion studies (Gerstmann, 1957; Gold et al., 1995; Mayer et al., 1999). The current study therefore directly compared the contribution of the two hemispheres during LRD. We expected (Hypothesis 1) LRD to rely on occipital, parietal and prefrontal regions, especially involving the angular gyrus and supramarginal gyrus (Arbuse, 1947). We further expected the activation to be dominantly left lateralized (Hypothesis 2), particularly for the angular gyrus (Hannay et al., 1983; Hirnstein et al., 2011). Furthermore, it was hypothesized that men would be more accurate and faster than women in egocentric as well as extra-egocentric LRD (Hypothesis 3). This sex difference was predicted to be associated with any of the following (Hypothesis 4): (a) more bilateral activation in women relative to men, (b) more prefrontal activation in women, and (c) parietal activation in men as a result of different strategies (and/or effort) applied (Butler et al., 2006). Finally (Hypothesis 5), we expect women with high levels of estradiol and/or

progesterone (in the follicular and midluteal cycle phase) to (a) perform lower on LRD, and (b) to show more bilateral activation pattern, as compared to women in menstrual phase and men.

2. Methods

2.1. Participants

Sixteen healthy women (mean \pm SD: 23.25 \pm 5.01 years) and fifteen healthy men (23.13 \pm 2.42 years) were tested three times on a LRD task during fMRI recordings. Only right-handed native Norwegian participants were included in the study. The mean laterality quotient was 93.33 (SD = 11.16) for women and 93.78 (SD = 10.23) for men, as tested by the Edinburgh Handedness Inventory (Oldfield, 1971). All women were tested in three different cycle phases: menstrual phase (cycle day 2-4), follicular phase (cycle day 8-12), and luteal phase (cycle day 20-22). To estimate women's cycle phases, individual length of the menstrual cycle was taken into account. A regular menstrual cycle with a mean cycle length of 26 - 32 days was required for participation. Participants were not pregnant and did not use hormonal contraceptives or other hormone regulating medicaments at the time of testing or for six months before testing. Time of day for testing deviated no more than three hours between intra-individual testing sessions, in order to reduce circadian variations in sex hormone levels (Ahn et al., 2011). To control for possible session effects, one third of the women started testing in menstrual phase, one third in the follicular, and one third in the luteal phase. Men were tested three times with one to two weeks between two testing sessions. To control for session effects, men were randomly assigned to three groups, equivalent to the female cycle phase groups. Participants gave their informed

consent according to the Declaration of Helsinki. The study was approved by the Regional Committee for Medical Research Ethics at the University of Bergen.

2.2. Hormone assays

Two saliva samples, one before the fMRI scan and one after, were collected during each session for the participants. An independent hormone laboratory (IBL international) analyzed the saliva samples for concentration of estradiol and progesterone. This was done by applying luminescence assays on an average amount of the two samples.

Sixteen participants were included for subsequent statistical analysis. Luteal progesterone levels served as an indicator of ovulation in women. Participants whose progesterone and estradiol levels were within expected ranges for the respective cycle phases, were included (see Table1). A repeated measures ANOVA was estimated on progesterone levels and revealed a significant effect of cycle phase ($F(2,30)=37.8$, $p<0.001$, $\eta^2=0.72$). Fishers LSD post-hoc test showed significant differences between the menstrual and luteal phase ($p<0.001$), and between the follicular and luteal phase ($p<0.001$). The repeated measures ANOVA on estradiol levels also revealed a cycle phase effect ($F(2,30)=6.48$, $p=0.004$, $\eta^2=0.3$). Fishers LSD post-hoc analysis revealed a significant difference between the menstrual and luteal phase ($p=0.001$), and the difference between the follicular and luteal phase approached statistical significance ($p=0.06$). Of the sixteen women, six started testing in their menstrual phase, five in their follicular phase, and five in their luteal phase.

Table1. Estradiol and progesterone levels from saliva samples in the women (n=16) during the menstrual, follicular and luteal cycle phase, are summarized in means, standard deviations, and range (in brackets).

Hormone in pg/ml	Menstrual Phase	Follicular Phase	Luteal Phase
Estradiol	2.7 \pm 1.3 (1.3-5.3)	3.6 \pm 1.5 (1.6-6.3)	4.5 \pm 1.6 (2.1-7.7)
Progesterone	53.2 \pm 17.8 (25.2-115)	57.3 \pm 30.4 (23.6-136)	191.4 \pm 93.8 (95.2-416.7)

2.3. Left-right discrimination task

The LRD task was adopted from Hirnstein et al. (2009). The participants were presented with pictures of pointing hands (See Figure 1) in various positions, and were asked to judge whether they saw a right or a left hand (LRD condition). In the control condition, the same stimuli were presented, but here participants were instructed to respond whether they saw the inner or outer side (palm or dorsum) of the hand.

The stimuli were divided into two categories: hands that were presented in a position a person sees his/her own hands when looking at them were categorized as non-rotated or egocentric. (see Figure 1, stimuli (a) and (b)). Pointing hands in unusual orientations in which a person normally does not see his/her own hands were categorized as rotated or extra-egocentric (see Figure 1, stimuli (c-h)). This categorization has been adopted from Hirnstein et al. (2009). Previous research revealed that all stimuli can induce LRD (Hirnstein et al., 2009). However, participants have previously shown to be more accurate on the egocentric stimuli, probably

because the extra-egocentric stimuli require mental rotation before the LRD can be done (Hirnstein et al., 2009).

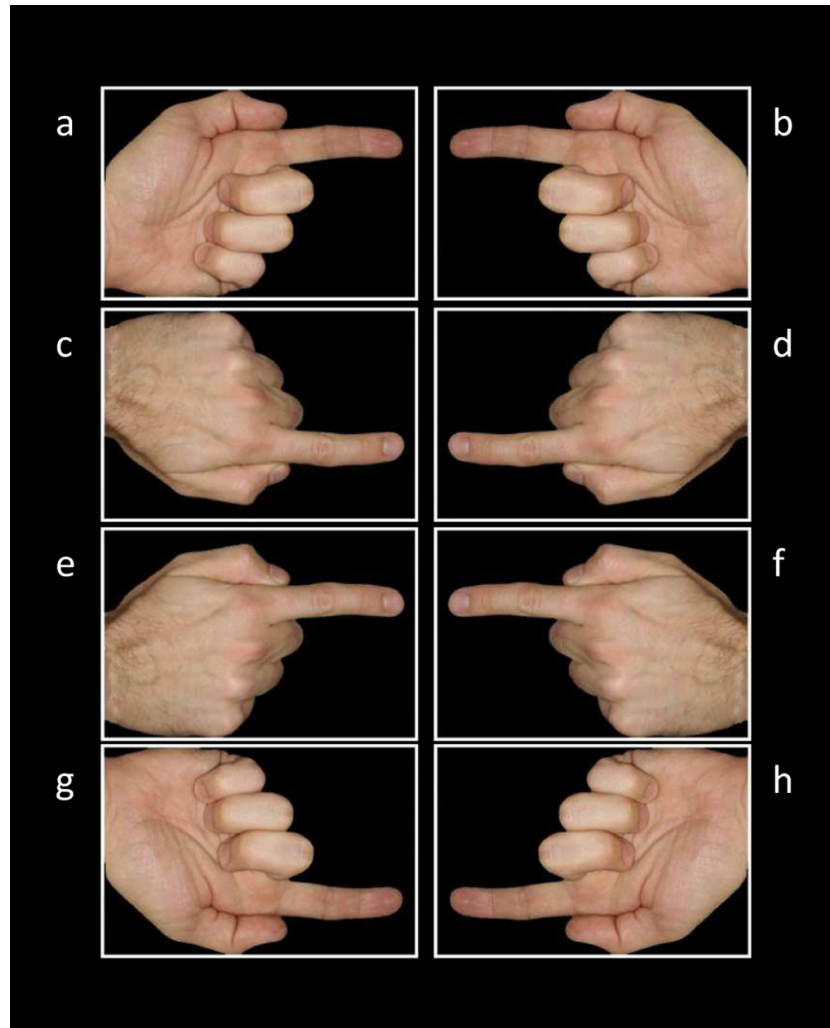


Figure 1. The LRD task involved eight stimuli. Stimuli (a) and (b) are egocentric. They are in a familiar position as this is usually how a person sees his/her hands. Stimuli (c), (d), (e), (f), (g), and (h) are extra-egocentric. Before performing LRD, they need to be mentally rotated into the egocentric position where they can be recognized as left or right hand.

Participants responded by button presses, using a response-grip held in the dominant, right hand. In the LRD condition, the thumb-button served as response for “right hand”, and the index-finger button for “left hand”. In the control condition the thumb was used to respond “dorsum” and the index-finger to respond “palm”. Before entering the scanner, participants were familiarized with the stimuli and task by a LRD pre-test.

The task was arranged in a pseudo-randomized block design. However, the timing of trials allowed for an event-related statistical analysis. The paradigm contained twelve blocks for the LRD condition and six blocks for the control condition, as well as six rest periods. Each block contained ten trials, and lasted for 28 seconds. In the control condition the presentation frequency was equal for all eight stimuli. In the LRD condition the two egocentric stimuli were presented 30 times each, and the six extra-egocentric stimuli were presented 10 times each. Hence, in total, the presentation frequency for egocentric and extra-egocentric stimuli was equal, ensuring comparable power for the egocentric and extra-egocentric condition. Each block was initiated by an instruction (displayed for 4500 ms), along with a reminder of which button to press for which response. For the experimental condition, the instruction was “Do you see a right hand or a left hand?”, and for the control condition: “Do you see the inside or the outside of the hand?”. Each trial started with a fixation cross (displayed for 250 ms) followed by an image of a pointing hand (each image displayed for 2000 ms). Participants were asked to respond to each stimulus during presentation time. Stimuli were presented via MR-compatible goggles and responses were given via fibre-optic response grips (Goggles and response grips from NordicNeuroLab; www.nordicneurolab.no). Stimulus presentation and button presses were controlled by E-prime (version 2.0) (Psychology Software Tools, Inc). The fMRI sequence lasted for 11 min and 20 s.

2.4. MR acquisition

Data were collected with a 3T GE-Signa MRI scanner. First, an anatomical T1-weighted image was acquired of each subject (3DT1 FSPGR, TR/TE/FA/FOV 7.9ms/3.2ms/11°/256mm, 256 x 256 scan matrix, 180 sagittal slices, voxel size 1 x 1 x 1 mm). For the following acquisition of functional images (EPI), 240 images were collected with whole brain coverage (GE-EPI, TR/TE/FA/FOV 2800ms/30ms/90°/220mm, 128 x 128 matrix, 35 sagittal slices, voxel size 1.72 x 1.72 x 3.5 mm).

2.5. Data analysis

The first three scans were treated as dummy scans and rejected in subsequent analysis. Pre-processing and statistical analysis were performed in SPM8 (Wellcome Trust Centre for Neuroimaging, www.fil.ion.ucl.ac.uk) implemented in Matlab R2009a (Mathworks, Sherborn, MA, www.mathworks.com). The data went through the pre-processing steps realignment (reference volume: the first EPI volume), unwarping, normalization of the anatomy (template image provided by the Montreal Neurological Institute, MNI) - resampled with a voxel size of 2×2×2 mm - and smoothing (FWHM: 8mm).

All statistical analyses were based on the general linear model (GLM) approach, implemented in SPM8 (Friston, 2003b; Friston et al., 1995). First, the trial-by-trial timing of egocentric, extra-egocentric, and control stimuli were modelled on a single participant level. During the estimation of this model, low-frequency drifts in the signal were removed using a high-pass filter of 360s. Trials were modelled with a duration of 0.8 TR. To regress out remaining

movement artefacts, the individual movement parameters were included in the design matrix as additional covariates. After model estimation, the contrasts Egocentric-Control and Extra-Egocentric-Control were estimated, and these individual contrasts were then subjected to a 2(Sex) x 3(Cycle Phase) x 2(Stimuli Set: egocentric vs. extra-egocentric) second-level ANOVA, using the factorial design set-up in SPM8 (testing hypotheses 1, 4b/c). An extension of this analysis including the additional factor Hand (left hand vs. right hand stimuli) is presented in the supplementary material (Figure S1). Individual total brain volume was implemented as covariate (last column in the design matrix) in the group analysis to make sure the results were not confounded by differences in brain size (Brodthmann et al., 2009). Estimates of individual brain volume were calculated using tissue probability maps in subject space, that were generated from each individual's structural T1 image by unified segmentation and normalization routines in SPM8 (Ashburner and Friston, 2005). Estimation of a Sex by Cycle Phase ANOVA on total brain volume showed significantly larger brains in men as compared to women ($F(1,29)=22.7$; $p<0.001$; $\eta^2=0.44$). (No other effects were significant).

In addition to the main and interaction effects tested by the ANOVA, t-contrasts were estimated in order to look for common activation for the egocentric and extra-egocentric stimuli as this would reflect a “pure” LRD, leaving out activation exclusively associated with mental rotation (Hypothesis 1). T-contrasts were therefore estimated separately for egocentric and extra-egocentric stimuli (across sex and cycle phase), and subsequently a global conjunction analysis was estimated with these two contrasts.

In addition, a post hoc analysis was conducted based on the results from the ANOVA. To see whether the sex difference in brain activation was predicted by behavior in men and women,

a ROI analysis was done. The cluster from the t-contrast of women-men (left MFG, eight voxels) was used as seed region. The definition of this cluster as ROI, and extraction of each participant's mean BOLD signal within this region was done using the MarsBaR (MARSeille Boîte À Région d'Intérêt) Toolbox. The extracted values of the BOLD signal were further averaged across cycle phase and condition for each subject, and correlated with corresponding averaged accuracy and reaction time data. The correlation was done separately for men and women.

In order to directly investigate LRD asymmetries in brain activation as well as sex differences and menstrual cycle effects in this asymmetry (Hypotheses 2, 4a, 5b), a separate analysis was performed following the procedure suggested by Friston (2003a). First, the individual contrast files (Egocentric-Control and Extra-Egocentric-Control) were normalized to a symmetrical template, using an individual realigned and normalized EPI image as source image. These files were then left-right flipped, and the flipped files were thereafter subtracted from the original symmetric files. Thus, new contrast files were created that contained the differences in activation between the left and right side. These contrast files were then subjected to a 2(Sex) x 3(Cycle Phase) x 2(Stimulus Set) ANOVA. To explore significant effects, ROIs were created from the significant clusters. These ROIs were used to extract activation values, in homotopic regions, from the symmetrically normalized files. In addition, a global conjunction analysis was estimated on the asymmetry maps to look for overall asymmetry across stimulus sets. T-contrasts estimated separately for egocentric and extra-egocentric stimuli were subjected to a global conjunction analysis. This reflects “pure” LRD, as activations exclusively associated with mental rotation are left out.

Results for all fMRI analyses were corrected for multiple comparisons (FWE correction) to $\alpha=0.05$. In addition, a cluster size threshold of five adjacent voxels was used. Significant regions were determined by plotting MNI coordinates (SPM output) into MRICron's AAL atlas.

In the same manner as for the fMRI data, the behavioral data were analyzed with two 2(Sex) x 3(Cycle Phase) x 2(Stimulus Set) ANOVAs, one for accuracy and one for reaction time data (testing hypotheses 3, 5a). Individual reaction times were calculated as the mean for correct trials. Data analysis was carried out with Statistica 12 software (Statsoft, Tulsa, OK, USA).

3. Results

3.1. Behavioral data

The 2(Sex) x 3(Cycle Phase) x 2(Stimulus Set) ANOVA (See Figure 2) calculated for accuracy rates revealed a main effect of Sex ($F(1,29) = 5.3, p = 0.03, \eta^2 = 0.16$), in which men performed more accurately than women. In addition, a main effect of Stimulus Set ($F(1,29) = 56.57, p < 0.001, \eta^2 = 0.66$) revealed higher accuracy for egocentric stimuli as compared to extra-egocentric. There was also an interaction of Sex and Stimulus Set ($F(1,29) = 8.24, p = 0.008, \eta^2 = 0.22$). Fisher LSD post-hoc testing showed a significant difference between egocentric and extra-egocentric stimuli in women ($p < 0.001$), and men ($p = 0.003$). For accuracy rates no other main or interaction effects were significant (all $F < 0.9, p > 0.27$). Moreover, there was a significant sex-difference for extra-egocentric ($p = 0.001$), but not egocentric stimuli ($p = 0.59$). The same ANOVA set-up on reaction times again revealed significant main effect of Sex ($F(1,29) = 5.88, p$

= 0.02, $\eta^2 = 0.17$) in which men responded faster than women. A main effect of Stimulus Set ($F(1,29) = 111.79$, $p < 0.001$, $\eta^2 = 0.79$) revealed that the participants responded faster in the egocentric stimuli as compared to the extra-egocentric stimuli.). No other main or interaction effects were significant (all $F < 2.2$, $p > 0.12$).

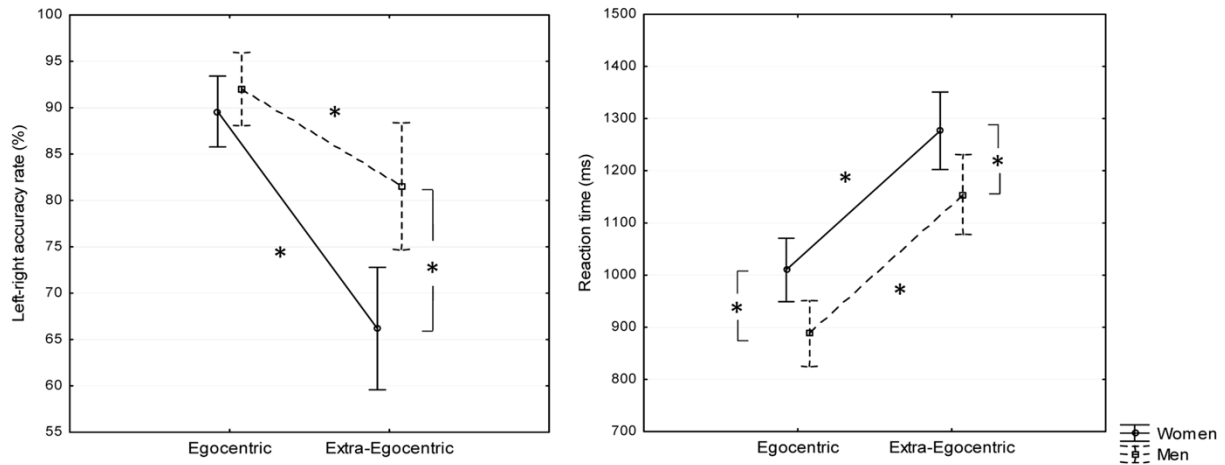


Figure 2. Behavioral sex differences in LRD. The graphs show accuracy and reaction time of men and women for egocentric and extra-egocentric stimulus processing, respectively. For details please refer to text. “*” indicate significant post-hoc pairwise comparisons (at $p < 0.05$). Error bars represent standard error.

3.2. fMRI data

The 2(Sex) x 3(Cycle Phase) x 2(Stimulus Set) ANOVA estimated on the fMRI data revealed a significant main effect of sex (F-contrast) at FWE correction, $p < 0.05$ (although it did not exceed the cluster threshold of five voxels), with higher activation for women in the left middle frontal gyrus (FWE thresholded t-contrast shown in Figure 3). A post-hoc region of interest analysis (ROI) was conducted to investigate whether the extracted values from left

middle frontal gyrus BOLD response correlated with the behavior data. Neither women nor men showed significant correlations between brain activation and accuracy rates (i.e., women $r(14) = -0.13$, $p = 0.64$; men $r(13) = -0.08$, $p = 0.78$) or reaction times (i.e. women $r(14) = 0.45$, $p = 0.08$; men $r(15) = 0.05$, $p = 0.85$), although the positive correlation for reaction time in women approached significance.

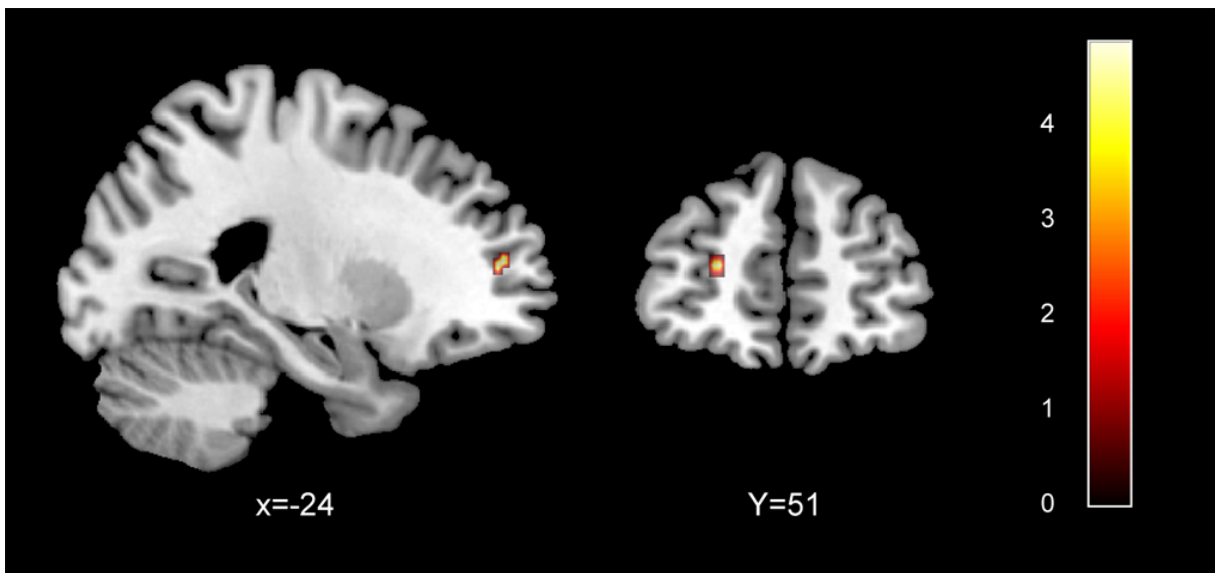


Figure 3. Neural basis of sex differences in LRD. Women showed stronger activation in left middle frontal gyrus as compared to men. Depicted is the t-contrast women-men (significant at $p < 0.05$, FWE-corrected; cluster size threshold of eight voxels). Coordinates (mm) are reported in MNI space. The color scale ranging from red to yellow represents t-values.

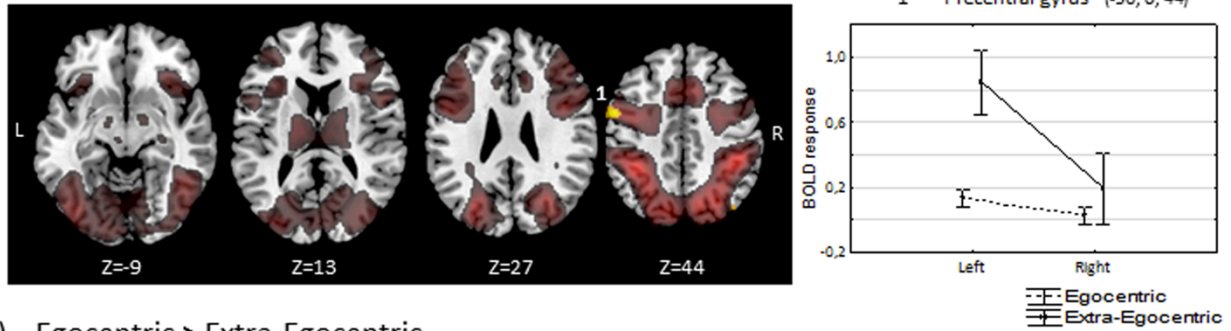
In addition, the main effect of Stimulus Set (see Fig 4, Table 2a/b) revealed that some regions were specifically involved in processing extra-egocentric vs. egocentric stimuli. Regions of higher activation in extra-egocentric stimuli as compared to egocentric were found in parietal, frontal, and occipital areas (see Figure 4, Table 2a). The largest cluster was found in the parietal

lobe including bilateral activation in inferior parietal lobe, supramarginal gyrus, precuneus, superior parietal lobe, angular gyrus, cuneus, fusiform gyrus, lingual gyrus, calcarine sulcus, middle and inferior occipital lobe, and cerebellum. The peak voxels of this cluster were located in left inferior parietal lobe, right supramarginal gyrus and left precuneus. A large cluster was also found in the prefrontal cortex involving bilateral activation in middle frontal gyrus, superior frontal gyrus, supplementary motor area, insula, inferior frontal gyrus triangularis, and operculum, precentral gyrus, and middle cingulate cortex. The peak activations for this cluster were located in the right middle frontal gyrus, left superior frontal gyrus, and right supramarginal gyrus. Additional clusters for the extra-egocentric stimuli were found in bilateral thalamus, and brainstem.

In addition, areas were found that showed stronger deactivations for extra-egocentric stimuli as compared to egocentric stimuli (see Figure 4, Table 2b). Noteworthy, activation for the same control condition has been subtracted for both egocentric and extra-egocentric stimuli. The largest cluster of deactivation was located in the medial prefrontal region with peak activation in bilateral medial frontal cortex orbital and superior, and left anterior cingulate cortex. The cluster extended into bilateral caudate nucleus, putamen, superior frontal gyrus, middle temporal gyrus, fusiform gyrus, hippocampus and parahippocampus, and right anterior cingulate cortex. In addition, eight more clusters were found: left angular gyrus; bilateral posterior cingulate cortex, middle cingulate cortex and paracentral lobule; Left middle temporal gyrus and inferior temporal gyrus; Right angular gyrus and inferior parietal lobe; Right inferior temporal gyrus and middle temporal gyrus; right parahippocampus and olfactory cortex; Left insula and rolandic operculum;

Right Insula, rolandic operculum and superior temporal gyrus. No other main or interaction effects were significant (all $F < 14.53$, $P_{(FWE-corr)} > 0.47$).

a) Extra-Egocentric > Egocentric



b) Egocentric > Extra-Egocentric

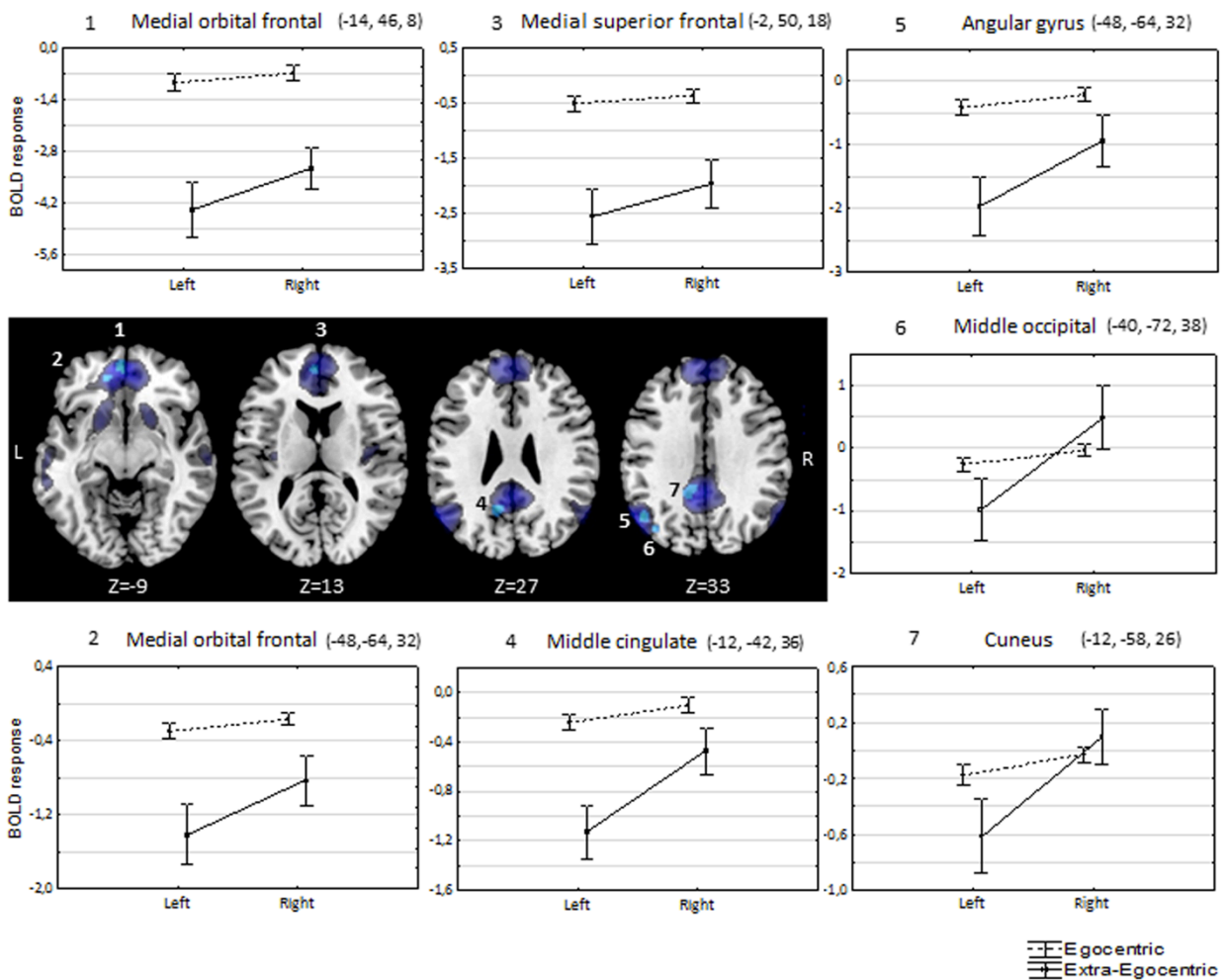


Figure 4. Extra-egocentric vs. egocentric stimuli. Results were thresholded at $p < 0.05$, cluster size of 5 consecutive voxels, FWE-corrected. a) Extra-egocentric stimuli show overall stronger activation in fronto-parietal network as compared to egocentric stimuli (depicted in red), as well as more leftward activation (asymmetry analysis; depicted in yellow); Slices shown in MNI coordinates system. b) Extra-egocentric stimuli show overall stronger deactivation in default mode network as compared to egocentric stimuli (depicted in blue), as well as more leftward deactivation (asymmetry analysis; depicted in light blue; slices shown in MNI coordinates). Note that the activations/deactivations are relative to the control condition. The graphs show BOLD response of left and right hemisphere for egocentric and extra-egocentric stimuli in areas where an asymmetry effect was found. The regions of asymmetry (light blue) are marked with numbers and refer to corresponding graphs. Error bars represent standard error. MNI coordinates (x, y, z) for these regions are given in brackets. Note that the values on the y-axis are different for the various regions. Negative values (BOLD responses) are interpreted as deactivations, however, note that the same control condition was subtracted from egocentric and extra-egocentric conditions prior to the comparison of the two stimuli set. Abbreviations: L – left; R – right.

Table 2. Main effect of Stimulus Set

a) Extra-Egocentric > Egocentric. Regions of stronger activation in Extra-Egocentric relative to Egocentric condition (see also Figure 4a).

Cluster size	F	Z	MNI coordinates (mm)			Side	Area	BA	Extending into
			X	Y	Z				
35051	209.08	>10	-36	-44	44	L	IPL	40	Bilateral AG, cerebellum, CS, cuneus, FFG, LG, IOL, MOL, SPL, L SMG, L SOL, R IPL.
	206.45	>10	42	-38	44	R	SMG	40	
	189.79	>10	-10	-74	50	L	Precuneus	7	
	181.34	>10	12	-72	48	R	Precuneus	7	
	170.96	>10	28	-68	48	R	SOL	7	
16948	183.02	>10	30	0	60	R	MFG	6	Bilateral IFGoper, IFGtri, MCC, PCG, L Insula, L MFG, R SFG.
	166.56	>10	-22	-4	56	L	SFG	6	
	123.99	>10	2	14	52	R	SMA	32	
	123.18	>10	32	24	-2	R	Insula	47	
	121.35	>10	-6	12	50	L	SMA	32	
2822	80.76	>10	-14	-10	8	L	Thalamus		
	63.34	7.24	12	-6	4	R	Thalamus		

	55.28	6.81	10	-16	8	R	Thalamus
111	32.68	5.33	-4	-22	-14	L	Brainstem
	29.73	5.10	6	-24	-22	R	Brainstem

Note: Results were thresholded at $p < 0.05$, cluster size of 5 voxels, FWE-corrected. Abbreviations: L – left, R – right, AG – angular gyrus, CS – calcarine sulcus, FFG – fusiform gyrus, IFG oper – inferior frontal gyrus operculum, IFG tri – inferior frontal gyrus triangularis, IOL – inferior occipital lobe, IPL – inferior parietal lobe, LG – lingual gyrus, MCC – middle cingulate cortex, MFG – middle frontal gyrus, MOL – middle occipital lobe, PCG – precentral gyrus, SFG – superior frontal gyrus, SMG – supramarginal gyrus, SMA – supplementary motor area, SPL – superior parietal lobe

- b) Egocentric > Extra-Egocentric. Regions that are deactivated, and more so in Extra-Egocentric relative to Egocentric condition (see also Figure 4b).

Cluster size	F	Z	MNI coordinates (mm)			Side	Area	BA	Extending into
			X	Y	Z				
6559	127.42	>10	0	52	-12	L&R	MOFL	11	Bilateral ACC, CN, FFG, HC, MTG, PHC, Putamen, SFG
	109.44	>10	-2	54	2	L	ACC	10	
	97.81	>10	4	46	-4	R	MOFL	10	
	90.23	>10	0	54	20	L	MSFL	32	
	75.79	7.82	10	52	46	R	MSFL	9	
977	121.18	>10	-56	-64	36	L	AG	39	

2959	99.43	>10	-2	-46	32	L	PCC	23	R PCC, L PCL
	89.41	>10	0	-26	46	L&R	MCC	23	
	39.41	5.84	2	-28	68	R	PCL	4	
549	69.89	7.56	-60	-14	-14	L	MTG	21	
	53.72	6.73	-48	-2	-36	L	ITG	20	
425	66.32	7.39	58	-64	28	R	AG	39	
	59.07	7.02	58	-56	44	R	IPL	40	
443	57.05	6.91	46	4	-44	R	ITG	20	
	56.81	6.90	62	-12	-16	R	MTG	21	
527	53.18	6.7	26	-10	-32	R	PHC	36	
	51.46	6.60	18	12	-14	R	OC	11	
170	36.63	5.64	-38	-16	4	L	Insula	48	
	32.62	5.33	-38	-16	20	L	RO	48	
332	32.12	5.30	40	-12	2	R	Insula	48	
	29.78	5.10	36	-22	20	R	RO	48	
	29.71	5.10	52	-6	4	R	STG	48	

Note: Results were thresholded at $p < 0.05$, cluster size of 5 voxels, FWE-corrected. Abbreviations: L – left, R – right, ACC – anterior cingulate cortex, AG – angular gyrus, CN – caudate nucleus, FFG – fusiform gyrus, HC – hippocampus, MCC – middle cingulate cortex, ITG – inferior temporal gyrus, IPL – inferior parietal lobe, MTG – middle temporal gyrus, MOFL – medial orbital frontal lobe, MSFL – medial superior frontal lobe, OC – olfactory cortex, PCC – posterior cingulate cortex, PCL – paracentral lobule, PHC – parahippocampus, RO - Rolandic operculum, SFG – superior frontal gyrus, STG – superior temporal gyrus. Note that the same control condition was subtracted from egocentric and extra-egocentric conditions prior to the comparison of the two stimuli set.

The global conjunction analysis based on the t-contrasts for egocentric and extra-egocentric stimuli (see Figure 5, Table 3), revealed thirteen clusters. The largest cluster was found on the right side covering parts of supramarginal gyrus, inferior parietal lobe and angular gyrus. A corresponding cluster was found on the left side of inferior parietal lobe only. Further, a right hemispheric cluster was found in precuneus, superior parietal lobe and superior occipital lobe, and a left sided cluster was found in the precuneus. In addition, seven more clusters on the right side were found: middle frontal gyrus and precentral gyrus; Calcarine sulcus; inferior frontal gyrus operculum; superior occipital lobe; and insula. Moreover, two clusters of deactivation were found on the left side in medial orbital frontal lobe and middle temporal gyrus. Deactivations are relative to the control condition which was the same for egocentric and extra-egocentric stimulus set.

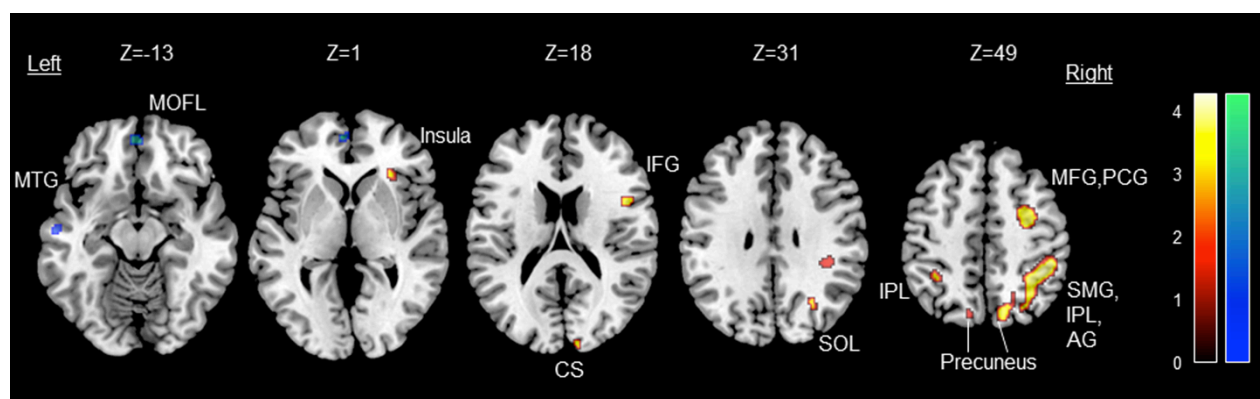


Figure 5. Neural correlates of LRD. Results thresholded at $p < 0.05$, cluster size of 5 voxels, FWE-corrected. Depicted are the results of the global conjunction analysis showing common activation for egocentric and extra-egocentric stimuli. Activations (T-values) are depicted in red-yellow scale, and deactivations in blue-green scale. Note that deactivations are relative to the control condition that was identical for egocentric and extra-egocentric stimuli set. Abbreviations: AG – angular gyrus, CS – calcarine sulcus, IFG – inferior frontal gyrus, IPL – inferior parietal lobe, MFG – middle frontal gyrus, MOFL – medial orbital frontal lobe, MTG –

middle temporal gyrus, PCG – precentral gyrus, SMG – supramarginal gyrus, SOL – superior occipital lobe.

Table 3. Brain activations associated with left-right discrimination, as revealed by the conjunction analysis of egocentric and extra-egocentric stimuli.

Cluster size	T	Z	MNI coordinates (mm)			Side	Area	BA
			X	Y	Z			
858	4.13	6.04	42	-36	42	R	SMG	40
	3.62	5.38	34	-48	48	R	IPL	40
	3.32	4.99	32	-58	50	R	AG	7
129	3.56	5.30	12	-70	46	R	Precuneus/SPL	7
	3.22	4.86	20	-60	46	R	SOL	7
304	3.54	5.28	30	0	58	R	MFG	6
	3.48	5.20	30	-8	48	R	PCG	40
82	3.44	5.15	6	-90	8	R	Calcarine	18
86	3.37	5.05	46	8	18	R	IFGoper	44
81	3.29	4.95	-36	-44	44	L	IPL	40
	3.17	4.80	-42	-40	40	L	IPL	40
27	3.25	4.90	28	-64	32	R	SOL	19
29	3.20	4.84	30	26	-2	R	Insula	47
8	3.14	4.75	-10	-74	50	L	Precuneus	7
72 DA	3.34	5.02	-2	54	-8	L	MOFL	11
12 DA	3.18	4.81	-58	-12	-14	L	MTG	21

Note: Results were thresholded at $p < 0.05$, cluster size of 5 consecutive voxels, FWE-corrected. Abbreviations: DA – deactivation, L – left, R – right, AG – angular gyrus, IFGoper – inferior frontal gyrus operculum, IPL – inferior parietal lobe, MOFL – medial orbital frontal lobe, MFG – middle frontal gyrus, MTG – middle temporal gyrus, PCG – precentral gyrus, SMG – supramarginal gyrus, SOL – superior occipital lobe, SPL – superior parietal lobe. Note that deactivations are relative to the control condition that was identical for egocentric and extra-egocentric stimuli set.

The 2(Sex) x 3(Cycle Phase) x 2(Stimuli Set) ANOVA for testing of brain asymmetry revealed a main effect of Stimuli Set (See Fig 4, Table 4). All clusters showed stronger leftward asymmetry, either in terms of stronger activation, or stronger deactivation, for extra-egocentric as compared to egocentric stimuli. One cluster, localized in precentral gyrus, showed stronger leftward activation for the extra-egocentric as compared to the egocentric stimuli. Eight clusters showed stronger leftward deactivation for extra-egocentric as compared to egocentric stimuli. Note that activation for the same control condition has been subtracted for both egocentric and extra-egocentric stimuli. These clusters were located in middle cingulate cortex, angular gyrus, medial orbital frontal lobe (two clusters), cuneus, calcarine sulcus, medial superior frontal lobe, and middle occipital lobe extending into angular gyrus. No other main or interaction effects were significant, and neither was the global conjunction analysis based on the t-contrast asymmetry maps for egocentric and extra-egocentric stimuli, (all $F < 22.84$, $P_{(FWE-corr)} > 0.21$).

Table 4. Asymmetry analysis. Regions that show stronger left lateralized activation in extra-egocentric stimuli as compared to egocentric stimuli (see also Figure 4).

Cluster size	F	Z	MNI coordinates (mm)			Asymmetry	Area	BA
			X	Y	Z			
61	50.17	6.53	-56	0	44	A LW	PCG	6
71	48.11	6.40	-12	-42	36	DA LW	MCC	23
25	40.35	5.90	-48	-64	32	DA LW	AG	39
33	36.56	5.63	-2	54	-8	DA LW	MOFL	11
41	34.78	5.50	-12	-58	26	DA LW	Cuneus/precuneus	23
	29.85	5.11	-10	-60	18	DA LW	CS	17
26	34.01	5.44	-2	50	18	DA LW	MSFL	32
33	33.15	5.38	-40	-72	38	DA LW	MOL/AG	19
12	31.40	5.24	-14	46	-8	DA LW	MOFL	11

Note: Results were thresholded at $p < 0.05$, cluster size of 5 consecutive voxels, FWE-corrected. Abbreviations: A – activation, DA – deactivation, LW – leftward, AG – angular gyrus, CS – calcarine sulcus, MCC – middle cingulate cortex, MOL – middle occipital lobe, MOFL – medial orbital frontal lobe, MSFL – medial superior frontal lobe, PCG – precentral gyrus. Note that the same control condition was subtracted from egocentric and extra-egocentric conditions prior to the comparison of the two stimuli set.

4. Discussion

The primary purpose of the current fMRI study was to investigate the neural basis of LRD in general, and of sex differences in particular. We also took into account the potential influence of women's sex hormonal state during the menstrual cycle. Areas specifically related to LRD across stimulus sets (Hypothesis 1, see Fig 5, Table 3) were found in occipital, prefrontal and parietal regions, including supramarginal gyrus, inferior parietal lobe, and angular gyrus of the right hemisphere and inferior parietal lobe of the left hemisphere. The asymmetry analysis (Hypothesis 2, see Fig 4, Table 4) showed leftward asymmetry for the extra-egocentric as compared to the egocentric stimuli, with leftward activation in precentral gyrus, and leftward deactivation in angular gyrus, posterior cingulate cortex and medial prefrontal cortex. The behavioral data (Hypothesis 3, Fig 2) revealed sex differences, regardless of menstrual cycle phases (Hypothesis 5a), for both egocentric and extra-egocentric stimuli in response time and accuracy. In accuracy, however, the sex difference was dominated by the stimulus set that required participants to mentally rotate the stimuli prior to LRD (extra-egocentric stimuli). In the fMRI data, women showed stronger prefrontal activation independently of whether the stimuli were egocentric or extra-egocentric (Hypothesis 4b/c, Fig 3).

4.1. Neural correlates of LRD

Brain areas involved in LRD, across egocentric and extra-egocentric stimuli (Hypothesis 1, see Fig 5, Table 3), were found in occipital, parietal and prefrontal areas, suggesting a larger network underlying LRD. In accordance with Hypothesis 1, the largest cluster was found in parietal regions where it stretches across superior parts of the

supramarginal gyrus via the inferior parietal lobe into the anterior part of the angular gyrus. On the left side, a corresponding cluster involved the inferior parietal lobe only. The angular gyrus involvement is consistent with previous studies (Gerstmann, 1957; Gold et al., 1995; Mayer et al., 1999) (although most studies point to left hemispheric dominance, see below for asymmetry discussion). However, since the activation is mainly centered around the supramarginal gyrus and inferior parietal lobe, we suggest that the parietal involvement in LRD is anatomically centered somewhat more anterior and inferior than what has previously been put forward. According to our results, there were also cases where lesions to supramarginal gyrus caused Gerstmann syndrome with symptom of left-right confusion (reviewed in Arbuse, 1947).

Considering that the study design controlled for mental rotation and verbal labeling (semantic processes), the parietal activation is likely not related to these cognitive functions. Another plausible prerequisite for successful LRD is an effective cognitive representation of the body (Auer et al., 2008). A degraded body image was also suggested by Gerstmann (1957) to be the very essence of Gerstmann syndrome. In line with this interpretation, Rousseaux, Honore, & Saj's review (2014) suggested that in healthy participants, egocentric body representations involve bilateral, though slightly right shifted, activation of posterior parietal regions (precuneus, superior parietal lobe, intraparietal sulcus), inferior parts of the parietal lobe, and to a lesser extent premotor areas and inferior frontal gyrus. This activation pattern is similar to the results of the current study, although we additionally found activation in the right superior occipital lobe and insula. Furthermore, lesions of the anterior parts of the parietal lobe, and especially the supramarginal gyrus were related to disturbances in body representations. Along the same lines, a study of neglect patients suggested that awareness of personal space (space of the body surface) relates to supramarginal gyrus and post-central

gyrus (and white matter medial to these regions), while awareness of extrapersonal space was related to frontal and temporal regions (Committeri et al., 2007). In sum the parietal activation is most likely related to awareness of body representations/personal space, or the matching of personal space onto external space.

4.1.1. Egocentric versus extra-egocentric stimuli

It is important to note that the activation patterns differed significantly between stimulus sets (see Figure 4, Table 2). Although differences between these two sets of extra-egocentric vs. egocentric stimuli have been shown before on the behavioral level (Hirnstein et al., 2009), the size of this effect is surprisingly large given that stimuli only differed in their orientation. Processing extra-egocentric stimuli was associated with higher frontoparietal activation as compared to the egocentric stimuli. This network has been previously associated with cognitively demanding tasks in general (Naghavi and Nyberg, 2005), and most likely reflects higher cognitive effort in processing extra-egocentric stimuli. This view is supported by the lower LRD behavioral performance in extra-egocentric as compared to egocentric stimuli. Furthermore, the extra-egocentric stimuli were associated with more deactivation in medial and lateral parietal regions (angular gyrus), and medial prefrontal regions. All areas are core regions of the default mode network (Raichle et al., 2001; Seghier, 2013), a network which has been found to be down-regulated during task performance (Fox et al., 2005; Raichle et al., 2001), and is related to inwards direction of attention (Qin and Northoff, 2011; Sestieri et al., 2011). Deactivation of default mode regions has previously been found to enhance with task difficulty, which might reflect increasing demands for reallocation of resources, and need for suspension of spontaneous thoughts (McKiernan et al., 2003).

4.1.2. Hemispheric asymmetry in LRD

The study is the first to directly test hemispheric specialization for LRD with fMRI (Hypothesis 2). The majority of previous studies have suggested a left-hemispheric dominance (Gerstmann, 1957; Gold et al., 1995; Hannay et al., 1983; Hirnstein et al., 2011; Mayer et al., 1999), while Auer et al. (2008) found more right-hemispheric activations. Auer et al., however, did not directly compare left and right hemisphere activation. Therefore, it is not possible to say whether the observed differences between left and right hemisphere in their study were significant (Liegeois et al., 2002; Westerhausen et al., 2014). Similar to Auer et al. (2008), the present study found a higher number of LRD-related activation clusters in the right hemisphere, including the angular gyrus. However, when specifically tested against the left hemisphere, there was no significant difference. In agreement with Auer et al. (2008), we can therefore conclude that LRD is not simply confined to the left hemisphere (or left angular gyrus) but also involves right parietal areas.

Although LRD in general (across stimulus sets) did not reveal any significant hemispheric asymmetries, the egocentric and extra-egocentric stimulus sets appeared to be processed differently by the left and right hemisphere. Extra-egocentric stimuli showed leftward asymmetry as compared to egocentric stimuli (see Figure 4, Table 4). We found leftward *activation* in precentral gyrus/middle frontal gyrus, a region that has previously been reported in mental rotation (Jordan et al., 2002). Furthermore, we found leftward *deactivation* in the angular gyrus as well as other medial parietal and medial prefrontal regions. Similarly, a review of navigation strategies suggests a hemispheric asymmetry difference between egocentric and extra-egocentric strategy in the precuneus, middle occipital lobe, and angular

gyrus, where extra-egocentric processing relates to less right-hemispheric processing as compared to egocentric strategy (Boccia et al., 2014). The increased left hemispheric involvement in extra-egocentric stimuli might be due to the spatial (mental rotation) nature of the stimuli. Although mental rotation in general has traditionally been associated with the right hemisphere (Corballis, 1997 for a review; but see Milivojevic et al., 2009), mental rotation of body parts are found to be processed bilaterally or dominantly in the left hemisphere (Parsons, 2003).

It is also worth mentioning that both left and right hand stimuli elicited bilateral activation patterns (see supplementary material; Figure S1). The result contradicts a previous hypothesis that suggests each hand to be primarily processed by the contralateral hemisphere (Parsons et al., 1998). More specifically the study by Parsons et al. found that the ability of split brain patients to identify left hand stimuli was higher when presented to the right hemisphere and vice versa. However, due to the properties of fMRI, we cannot in the present study be certain that both hemispheres are actually crucial in processing of the respective left and right hand stimuli.

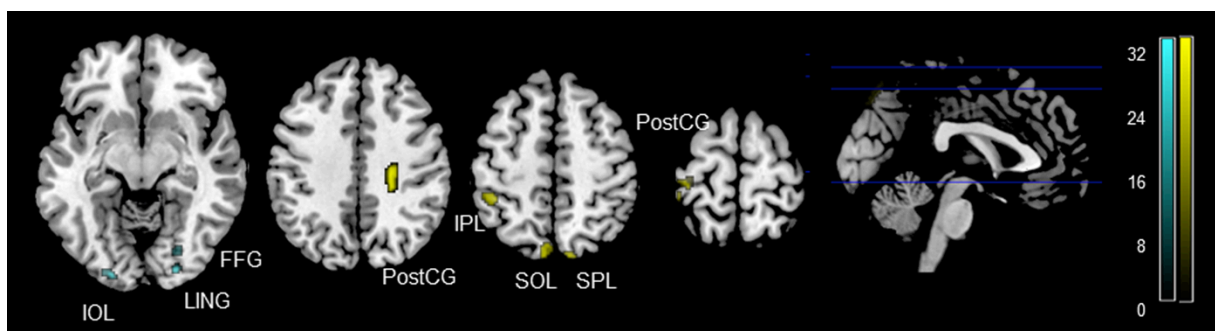


Figure S1. Left vs. right hand. An additional analysis was conducted according to the idea that the participants mentally rotate their own hands and match them onto the stimuli, and therefore would use more left hemispheric resources to rotate the right hand and vice versa (Parsons et al., 1998). The analysis was conducted including a fourth variable, Hand (making a Sex(2) x Cycle Phase(3) x Stimulus Set(2) x Hand(2) ANOVA), where left hand stimuli and right hand stimuli were considered separately. Results were thresholded at $p < 0.05$ (FWE-corrected), cluster size of 5 voxels. Activation differences were found in the following regions (in brackets: MNI coordinates (x, y, z) for the peak voxel; cluster size; and F value). Higher activation for right hand as compared to left hand stimuli was found in left superior occipital lobe (SOL; -6, -84, 48; 118 voxels; $F=35.07$), white matter medial to right postcentral gyrus (PostCG; 22, -24, 38; 100 voxels; $F=32.56$), left inferior parietal lobe (IPL; -44, -40, 56; 101 voxels; $F=28.79$), right superior parietal lobe (SPL; 10, -80, 54; 22 voxels; $F=26.65$), and left postcentral gyrus (PostCG; -34, -28, 70; 19 voxels; $F=26.03$). Higher activation for left hand as compared to right hand was found in left inferior occipital lobe (IOL; -22, -92, -10; 15 voxels; $F=27.76$), right fusiform gyrus (FFG; 24, -76, -8; 14 voxels; $F=26.12$), and right lingual gyrus (LING; 24, -88, -10; 10 voxels; $F=25.93$). The results do not provide support to Parson et al. (1998), as both set of hands show bilateral activation patterns. We cannot, however, rule out that the results were confounded by the fact that responses were given with the right hand only. The research question might, therefore, be worth investigating further in future studies.

4.1.3. LRD and the (left) angular gyrus

It was expected (Hypothesis 1, 2) that particularly the (left) angular gyrus is involved in LRD (Gold et al., 1995; Hirnstein et al., 2011). Left angular gyrus was instead found to deactivate during LRD (leftward deactivation for extra-egocentric stimuli, see Figure 4b). However, a small anterior dorsal part of the right angular gyrus was found activated during LRD across egocentric and extra-egocentric stimuli (see Figure 5). This might imply that there are anterior-dorsal and posterior-ventral sub-regions within angular gyrus that are respectively activated or deactivated during the task. Seghier (2013) described similar sub-regions for the left angular gyrus: An anterior-dorsal region which is related to ‘bottom-up’ processes, such as semantic search (also in LRD), and a posterior-ventral region, which was found to be associated with the default mode network. The lack of left angular gyrus

activation in LRD in the current study (see Figure 5, Table 3) might therefore indicate that the control condition, to which the experimental conditions were contrasted, depend equally much on semantic processing as the LRD. Whereas the LRD conditions required labeling of left and right hands, the control condition involved labeling of palm and dorsum of the hands. In comparison to Seghier (2013), the subregion of the right angular gyrus found activated in the current study overlaps with Seghier's anterior dorsal region (described for the left hemisphere). The right angular gyrus has been suggested important in other functions underlying LRD such as visual attention (Seghier, 2013) and own-body perceptions (Blanke et al., 2002). Regarding our deactivated posterior-ventral region, it overlaps partly with both anterior and posterior regions as described by Seghier (2013), with the peak voxel being located in Seghier's ventral region. Similarly, we interpret the deactivated left angular gyrus as part of default mode network due to the co-deactivation of other typical default mode areas (see above for further discussion of default mode network).

4.2. Sex differences in LRD

Several previous behavioral studies on LRD used tasks that involved mental rotation (Ofte and Hugdahl, 2002; Snyder, 1991). Jordan et al. (2006) concluded that this might account for pronounced sex differences observed in these studies. Studies on mental rotation usually find a sex difference with an effect size around 0.6 standard deviation (Voyer et al., 1995). However, two recent LRD studies revealed lower LRD performance in women regardless of mental rotation in the tasks (Hypothesis 3) (Hirnstein et al., 2009; Ocklenburg et al., 2011). In the current study, men responded faster to both extra-egocentric and egocentric stimuli (see Figure 2). In addition, however, this study also found that men responded more accurately than women especially when processing extra-egocentric stimuli. This suggests that sex differences in LRD performance occur independently of mental rotation, though mental rotation can increase the sex difference in LRD performance.

In line with the behavioral data a sex difference was found in brain activation (fMRI data) during LRD across stimulus set. It was, however, small and must be interpreted with care. Specifically, women showed slightly higher activation in the left middle frontal gyrus as compared to men (Hypothesis 4b, see Figure 3). The results are in line with a higher prefrontal activation in women as compared to men in visuospatial tasks, such as mental rotation (Butler et al., 2006; Hugdahl et al., 2006; Thomsen et al., 2000; Weiss et al., 2003). The higher PFC activation in women found in the current study might suggest (a) that more effort/brain capacity is needed because women struggle more in LRD (although using a similar neurocognitive strategy as men), or (b) a divergent strategy for women in solving the task. Butler (2006) suggests that the higher prefrontal activation in women, and parietal/sensory activation in men during mental rotation reflect that women perform the task

by more effortful “top-down” control, whereas men rely more on automatic “bottom-up” processes. The current study cannot, however, support (Hypothesis 4c) more parietal involvement in men (but see Hannay et al., 1983). Similar to Butler et al., others have argued that higher left prefrontal activation in women reflects a verbally mediated categorical spatial encoding strategy in women (Hugdahl et al., 2006; Pezaris and Casey, 1991). The correspondences of the sex differences observed in LRD and other visuospatial tasks might suggest that the essence of sex difference in LRD is of a visuospatial character. It is also important to note that the individual BOLD responses in the left middle frontal gyrus did not correlate with LRD accuracy or reaction times. However, for women only, the correlation with reaction time approached significance, which may indicate that the middle frontal gyrus is not beneficial for LRD.

Although women performed lower on the LRD task, the current study did not find any support for idea that sex differences in LRD are related to a more bilateral brain organization in women (Hypothesis 4a). Similarly, a recent TMS study (Hirnstein et al., 2011) found men and women to be equally affected by rTMS over the left angular gurus.

In contrast to Hypothesis 5, we did not find evidence for menstrual cycle-related modulation of women’s LRD performance or brain activation during LRD task, in spite of the carefully validation of cycle phases. The result contradicts studies suggesting sex-hormonal effects on women’s spatial abilities and their underlying brain organization (Hausmann and Güntürkün, 2000; McCormick and Teillon, 2001; Schoning et al., 2007). The literature is however inconsistent in this respect (e.g. Liben et al., 2002), and some studies rather suggest testosterone to be the main steroid hormone modulating spatial abilities and sex differences in spatial abilities (Aleman et al., 2004; Hooven et al., 2004).

4.3. Conclusion

The findings are in line with previous studies on LRD regarding the behavior data, and suggest that LRD is independent of mental rotation. The findings are less clear when looking at the neuroimaging results. The activation patterns in men and women across condition overlap to a large extent, regardless of the tested women's cycle phases. The only difference was found in the prefrontal cortex. Whether this small difference can explain the pronounced sex difference in LRD performance remains an open question. However, these findings might reflect that women use more top-down control in LRD. The results also show that LRD involves a bilateral network with parietal dominance, and not particularly the left angular gyrus, although the left hemisphere becomes more involved when the task involves more demanding extra-egocentric processes.

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