Striatal volume decrease after pregnancy and changes in navigation strategy

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Abstract

Pregnancy is accompanied by prolonged exposure to high estrogen levels. Animal studies have shown that estrogen influences navigation strategies and, hence, affect navigation performance. Navigation has been conceptualized as either relying on a hippocampus-based allocentric strategy or a striatum-based egocentric strategy. High estrogen levels have been related to increased use of allocentric strategies and decreased egocentric navigation performance. In humans, associations between hormonal shifts and navigation strategies are less clear. This study compared 30 peripartal women to an age-matched control group on whole-brain gray matter volume and allocentric versus egocentric navigation performance. Navigation performance was assessed during the last month of pregnancy, whereas structural brain parameters were assessed shortly after delivery. Relative to controls, pregnant women performed less well in the egocentric condition of the navigation task, but not the allocentric condition. A whole-brain group comparison revealed smaller left striatal volume (putamen) in the peripartal women. Across the two groups, left striatal volume was associated with superior egocentric over allocentric performance. Overall, these findings suggest that human pregnancy is accompanied by structural brain changes in navigation-related neural systems and concomitant changes in navigation strategy.

1. Introduction

Many studies have shown that variations in gonadal hormones in female animals –in particular estrogen– lead to structural brain changes, and to changes in behavior (Darnaudéry et al., 2007; DeVoogd & Nottebohm, 1981; Fader, Hendricson, & Dohanich, 1998; Galea et al., 2000; Galea & Kavaliers, 1995; Gibbs, 2000; Korol, 2004; Luine & Frankfurt, 2012; Pawluski, Brummelte, Barha, Crozier, & Galea, 2009; Woolley & McEwen, 1993; Woolley, 1998). Endogenous estrogen fluctuates naturally during the estrous cycle, peaks during pregnancy, and declines at menopause. Effects of varying estrogen levels therefore influence virtually all females during different phases of the lifespan. The hippocampus is one of the main targets of estrogen action in the brain, and its structure and function is affected by estrogen variation (McEwen, 2002; Pawluski et al., 2009). Together with the striatum, the hippocampus plays a crucial role in spatial learning and navigation (Keefe, Burgess, Donnett, Je, & Maguire, 1998; McDonald & White, 1994). The striatum also contains estrogen receptors, and it`s function is modulated by estrogen (Hartesveldt & Joyce, 1986; Küppers & Beyer, 1999). It appears that estrogen also regulates the relative contributions of striatal and hippocampal structures to spatial learning, at least in rodents (e.g., Daniel & Lee, 2004).

To understand how estrogen affects navigation, it is important to disentangle hippocampal and striatal contributions to spatial learning. While learning to navigate in a maze, navigators can associate motor responses with particular environmental cues and later react in response to these cues, resulting in an egocentric strategy, also called response learning (Kesner, Farnsworth, & DiMattia, 1989; Restle, 1957). Alternatively, navigators can make use of associations between landmarks and places to build a cognitive map. This process is referred to as an allocentric strategy, or place learning (Kesner et al., 1989). Whereas the striatum is involved in stimulus-response learning and egocentric strategy use (Packard, 2009), the hippocampus contains place cells required for allocentric navigation (Keefe et al., 1998). A large number of studies points to a competitive relationship between hippocampus-dependent versus striatum-dependent spatial learning strategies (e.g., Devan, Goad, & Petri, 1996; McDonald & White, 1994; Packard, White, & Ha, 1978), such that impairments of the hippocampus are associated with increased dependence on striatum-based strategies, and vice versa.

Korol and colleagues showed that estrogen differentially influences place and response learning by shifting the relative contributions of the hippocampus and striatum during learning (Korol & Kolo, 2002; Korol, 2004). Further studies replicated and extended this finding, revealing that high estrogen levels foster hippocampus-dependent (place) strategies and decrease performance in striatum-dependent tasks, whereas low estrogen levels facilitate the use of striatum-dependent strategies (Daniel & Lee, 2004; Galea et al., 2001; Zurkovsky, Brown, Boyd, Fell, & Korol, 2007). Given that the largest shifts in endogenous estrogen levels in humans appear during pregnancy we set out to explore navigation performance shortly before delivery and navigation-related brain structures shortly after delivery. Based on the animal literature we expected that the peripartal period would be accompanied by alterations in hippocampal-dependent learning strategies relative to non-pregnant women (Pawluski, Vanderbyl, Ragan, & Galea, 2006). In line with this hypothesis, pregnant rats have been shown to perform better in place-learning tasks involving the hippocampus than non-pregnant rats (Pawluski et al., 2006).

Comment [jmw1]: Maybe insert: "in rats"

Despite the strong body of literature on estrogen affecting navigation strategies in animals, almost nothing is known about the estrogen-navigation association in humans. The dissociation between hippocampus-based allocentric strategies and striatum-based egocentric strategies also holds in human navigation (Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; Wolbers & Hegarty, 2010). Estrogen effects on the human brain have only begun to be studied and results are far from complete. Initial structural magnetic resonance imaging (MRI) studies have found hippocampal structural plasticity between high-estrogen and low-estrogen phases of the menstrual cycle (Protopopescu et al., 2008; Lisofsky et al., submitted). These results indicate at least partly parallel effects of estrogen on human and animal brains.

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Or … and our understanding is far from being comprehensive?

Comment [jmw3]: …indicate that estrogen affects human and animals brains in similar ways ?

To our knowledge, no study thus far has investigated how variations in estrogen relate to navigation strategies in humans. This might be due to the difficulty to manipulate or observe human estrogen changes that are large enough to potentially affect brain and behavior to a measurable extent. Pregnancy is one instance of naturally occurring high estrogen level change. This event bears the potential to reveal whether hormonal shifts in human females are associated with alterations in the neural substrates and learning strategies underlying

navigation performance. No study so far has investigated navigation strategy or performance differences in relation to human pregnancy, but pregnancy-related differences in other cognitive abilities, such as memory, have been addressed (e.g., Henry & Rendell, 2007).

The present study had two main goals: First, to explore navigation strategies in pregnant women; second, to relate these strategies to alterations in brain structure observed shortly after delivery. We expected differences in route learning performance in pregnant relative to non-pregnant women. Specifically, we hypothesized a shift towards allocentric strategies during pregnancy, that is, lower performance in the egocentric condition and better performance in the allocentric condition relative to the control group. We also expected pregnancy-related volumetric alterations in hippocampal and potentially striatal volume. Here, we expected that the hypothesized shift towards allocentric strategies during pregnancy would be associated with increased hippocampal volume, decreased striatal volume, or both.

2. Methods

Participants

Thirty healthy pregnant women participated in the study (age: 28.03 (±3.33), mean years of education: 18.58 (±2.79)). All of the women in the peripartal group have never been pregnant before (>8 weeks of pregnancy). A group of thirty naturally cycling women that have also never been pregnant before was recruited as the control group (age: 27.97 (±3.37), years of education: 19.35 (±2.71)). None of the women in the control group used hormonal contraceptives during the six month prior to study participation and within the study phase. None of the participants had a history of neurological or psychiatric conditions or drug/alcohol abuse. The study was conducted according to the Declaration of Helsinki, with approval from the Ethics Committee of the German Society for Psychology.

Design and Procedure

Participants were tested with a number of cognitive tasks and questionnaires. The women in the peripartal group were tested during the last month of pregnancy. The assessment was scheduled based on the expected date of delivery. During the session, the women provided three saliva samples. The MRI assessment was delayed to the first two months following delivery. For the control group, the imaging and cognitive measurements were scheduled on two days within the early follicular phase of their menstrual cycle (1–10 days after onset of menses). The procedures during the cognitive and imaging session were the same for both groups.

Hormonal assessment

Saliva samples were collected using SaliCaps collection devices (IBL-International, Hamburg, Germany), which are validated for sampling of steroid hormones. To account for the pulsative secretion of estrogen, we collected three samples spread over the two hours testing time and pooled them afterwards, to minimize the effect of short-term fluctuations of hormone concentrations. Immediately after collection, saliva samples were frozen and stored at -25°C. The estrogen concentrations were determined by a commercial company (IBL-International, using IBL Saliva Imunoassay -17ß-Estradiol Saliva ELISA kit). Saliva samples

were analyzed for all women in the peripartal group (N=30) and a subgroup of women in the control group (N=14). A two-sample t-test was used to compare estrogen levels between the two groups.

Cognitive tasks and questionnaire

We used a number of memory tasks, assessing episodic verbal memory (word-list recall (Schmiedek, Lövdén, & Lindenberger, 2010), word-non-word cued recall (Mårtensson & Lövdén, 2011) and face-name cued recall (Mårtensson & Lövdén, 2011) as well as working memory (dual-2-back; Jaeggi et al., 2010) and object location memory (Schmiedek et al., 2010). Different tasks measuring spatial abilities were used, assessing mental rotation (Vandenberg & Kuse, 1978), spatial orientation (Guilford & Zimmerman, 1948; Gramann, Müller, Eick, & Schönebeck, 2005) and perspective-taking (Hegarty, 2004). Executive functioning was assessed with a task-switching paradigm (King, Colla, Brass, Heuser, & von Cramon, 2007).

In addition the Navigation Strategy task measuring route learning performance was used (Wiener, de Condappa, Harris, & Wolbers, 2013). A detailed description of the task can be found in the reference article. In the Navigation Strategy task, participants had to learn a route consisting of four four-way intersections. Each intersection is characterized by two specific landmarks at the diagonal opposite corners of the intersection that support the acquisition of route knowledge. In the training trials, the participants passively observe the correct way through the maze on the screen. In the test trial, participants approach an intersection either from the same direction as during the training phase (same direction trials, SD) or they approach the intersection from another arm (different direction trials, DD). In both conditions they have to indicate how the original route proceeded from there. The two conditions can be solved with different navigation strategies. The SD condition can be solved by solely relying on an egocentric strategy, that is, by having associated the direction of turn with the landmarks. The DD condition, in contrast, requires processing the configuration of landmarks and therefore relies on an allocentric navigation strategy. Performance was measured as accuracy (percent correct responses) in each of the two conditions. The performance difference between SD and DD trials (Navigation Task Difference score) was computed to index the benefit for a given individual in trials that can

be solved based on an egocentric strategy compared to trials that afford an allocentric strategy. Performance differences between the groups were analyzed by two sample t-Tests with an alpha level of 0.05. Statistical outliers were excluded before analysis (outliers were defined as values exceeding the 1st and 3rd percentile by more than 1.5 times the interquartile range).

The 10-item Edinburgh Postnatal Depression Scale (Cox & Sagovsky, 1987) was used to assess depressive symptoms. It was administered on each measurement occasion to all participants.

MRI data acquisition

MRIs were acquired using a 3T Magnetom Tim Trio MRI scanner system (Siemens Medical Systems, Erlangen, Germany) using a 12 -channel radiofrequency head coil. High-resolution anatomical images were collected using a T1-weighted 3D MPRAGE sequence (TR = 2500 ms, TE = 4.77 ms, TI = 1100 ms, acquisition matrix = 256×256×192, sagittal FOV = 256 mm, flip angle = 7°, voxel size = 1.0×1.0×1.0 mm^3).

MRI Data analysis

Anatomical data were processed by means of the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html) with default parameters by Gaser and the SPM8 software package (http://www.fil.ion.ucl.ac.uk/spm). The VBM8 preprocessing involves bias correction, tissue classification, and registration. The 'nonlinear only' modulation was applied in order to preserve the volume of a particular tissue within a voxel by multiplying voxel values in the segmented images by the Jacobian determinants derived from the spatial normalization step. In effect, the analysis of modulated data tests for regional differences in the absolute amount (volume) of GM. Finally, images were smoothed with a full-width half-maximum kernel of 8 mm. Statistical analysis was carried out by means of whole-brain comparison of GM volume between the two groups. Age and total intracranial volume were entered as covariates of no interest. The resulting maps were thresholded with $p<0.0001$ and a statistical extent threshold combined with a non-stationary smoothness correction were applied. After computing the whole-brain analysis, the GM values for each participant in the statistically significant regions were extracted by means of MarsBaR region of interest

toolbox for SPM (http://marsbar.sourceforge.net/) and correlated with behavioral performance (Pearson correlations).

3. Results

Sample description:

The mean time between the cognitive assessment during the last weeks of pregnancy and day of delivery in the peripartal group was 22.3 (±9.3) days. The imaging measurement took part on average about 33.5 (±8.1) days after delivery. The mean distance between the two sessions for the peripartal group therefore was 55.8 (±12.7) days. Except for three participants, the cognitive and imaging session of participants in the control-group took part within one week. The two groups did not differ with regard to age and educational status (p>0.1) or to their scores on the Edinburgh Postnatal Depression Scale (p>0.1 for both time-points).

Hormonal data:

Estrogen was significantly elevated in pregnant women compared to the control group (154.64(±61.69) pg/ml pregnant women; 10.04(±6.56) pg/ml control group; $t(42)=16.18$, $p<0.001$). Given their non-normal distribution, estrogen scores were log-transformed before analysis.

Cognitive tasks:

The groups did not differ reliably in their performance on the memory, spatial and executive functioning tasks ($p > 0.05$).

Navigation Strategy task data for two participants in the pregnant group were missing due to technical problems. Women in the peripartal group performed significantly less accurate in the SD condition of the Navigation Strategy task (82% vs 90% $t(53) = -2.22$; $p = 0.031$). However, the groups did not significantly differ in their DD performance, resulting in a significant group by condition interaction ($F(1,50) = 4.93$; $p = 0.031$; Figure 1).

MR data:

A VBM whole-brain between groups comparison revealed that GM volume in two regions within the left striatum (putamen) were smaller in the peripartal group than in the control group (x = –30, y = –17, z = –2; x = –18, y = 6, z = –6; $p < 0.0001$, cluster threshold = expected voxels per cluster, k > 46, corrected for non-stationary smoothness; Figure 3). When the threshold was lowered to $p < 0.005$, the striatal GM decreases were observed bilaterally (x = 20, y = –15, z = –11). There were no regions showing larger GM volumes in the pregnant group. Estrogen levels in the peripartal group (saliva samples were collected in late pregnancy) correlated negatively with GM probability in the posterior putamen region (r = –.44, p = 0.016).

To further explore this finding, GM volumes of the left and right putamen and the left and right hippocampus were extracted. Regions of interest were based on the automated anatomical labelling (AAL) atlas (Tzourio-Mazoyer et al., 2002). Two sample t-tests on these data showed that the peripartal group had lower GM volumes of the left and right putamen in than the control group ($t(58) = 3.08$, $p = 0.003$), whereas group differences for the left and right hippocampus were not reliable ($p > 0.05$). The GM differences between hippocampus and putamen differed significantly between the groups with greater difference scores (favoring the hippocampus) in the peripartal group ($t(58)=2.72$, $p=0.009$).

Relationship between MR and cognitive data:

GM probability in the left striatum (the region showing significant differences between the groups in the whole-brain comparison) correlated positively with the Navigation Task Difference score (SD-DD performance) in the total sample ($r = 0.30$, $p = 0.033$; Figure 4). Participants with greater striatal GM volume showed a more positive Navigation Task Difference Score, indicating a greater benefit associated with the egocentric task condition (egocentric prevalence). This linear association was not present when assessed within the peripartal group ($r = .04$, p =0.850), but reliably different from zero in the control group (r = 0.40, $p = 0.043$; difference between the two correlations: z = 1.3 p = 0.194). In addition, the ratio of hippocampal (left and right) over striatal (left and right putamen) GM correlated positively with allocentric task performance ($r = 0.3$, $p = 0.029$; Figure 5). A larger ratio was

related to better performance in the allocentric condition. That association was not reliable when analyzed within the peripartal group (r = 0.18, p = .359) and trend-wise significant in the control group r = 0.35, p = 0.070; difference between the two correlations: z = 0.64 p = 0.522).

4. Discussion

We investigated navigation performance in pregnant and non-pregnant women in relation to whole-brain structural differences observed between the groups. Pregnant women showed lower performance than non-pregnant women in the egocentric condition of a route learning task, but did not differ in the allocentric condition of the same task. Within the first two months after delivery, left striatal gray matter volume was significantly lower in the postpartal women than in the non-pregnant women. The performance difference between the ego- and allocentric condition correlated positively with gray matter volume in the striatum. Taken together, these results are consistent with the hypothesis that pregnancy leads to structural changes in navigation-related neural systems, and that these changes influence navigation performance.

As expected, we found that women's route learning performance was altered during pregnancy. However, this alteration was limited to performance impairments in the egocentric condition of the Navigation Strategy task. We did not observe significant differences in any of the other spatial memory tasks or spatial orientation tasks. The selectivity of the observed group differences may suggest that pregnancy does not affect spatial abilities in general, but exerts a rather specific effect on route learning. Route knowledge is often conceptualized as a series of recognition-triggered responses in which environmental cues or landmarks are associated with motor responses or movement directions (Waller & Lippa, 2007). The Navigation Strategy task was the only task assessing *learning* as a function of spatial orientation strategy, bearing close resemblance to tasks used in animal studies for investigating strategy changes in navigation.

We interpret the Navigation Strategy task results as a shift in strategy use, rather than solely a performance difference in the egocentric condition of the task. The egocentric condition is less difficult than the allocentric condition, as participants approach the way-finding decision points from the same direction as during learning. It is therefore an unusual pattern to find decreased performance in the easier, but not in the more difficult condition. If pregnancy-related performance differences would reflect general problems in memorizing the route, pregnant women would also show lower performance in the allocentric condition of the

task. Memory performance was also tested with a variety of other tasks, none of which indicated general decrements in memory performance in pregnant women. Hence, we suggest that the observed pattern of group differences reflects a shift away from egocentric processing in the group of peripartal women. If a participant strongly relies on an allocentric learning strategy, which requires processing the spatial configuration of landmarks at the intersection together with the arm in which the route continues, she might be worse in remembering the simple stimulus-response association that is sufficient to solve the task in the egocentric condition correctly. Accordingly, the benefit from approaching intersections from the same direction as during learning would be reduced. The performance in the allocentric condition, on the other hand, would be comparable to the one in the egocentric condition. This pattern was observed in the peripartal group. The strategy shift is captured best by the performance difference between egocentric and allocentric conditions, with higher difference scores indicating a stronger benefit from or preference for egocentric compared to allocentric processing. The direction of this strategy shift is in line with previous results on estrogen's influence on navigation strategies in animals. In rats, estrogen treatment leads to a bias towards hippocampal-based (allocentric) strategies, even when this strategy is disadvantageous in the given context (Daniel & Lee, 2004; Packard et al., 1978).

As hypothesized, we observed differences in neural structure within the navigation network between the two groups. Postpartal women had significantly lower volume in the left putamen, which is located within the striatum. Contrary to expectations, we did not observe significant group differences in hippocampal gray matter volume. Perhaps, our whole-brain measures were not able to uncover fine-grained differences in hippocampal subfields. The observed volumetric differences in the striatum are generally in line with our assumptions of pregnancy-related changes in navigation brain networks. We cannot draw further conclusions about the reasons for these differences, or the neural mechanisms that underlie them. A wide range of animal studies has shown peripartal plasticity of the female brain (Hillerer, Jacobs, Fischer, & Aigner, 2014). In humans, first evidence confirms brain structural alterations during pregnancy (Oatridge & Holdcroft, 2002), but whether these changes are exclusively caused by hormonal changes is unknown. Longitudinal work is needed to ascertain whether the observed group differences in striatal volume are related to continued

exposure of high estrogen levels during pregnancy. The negative correlation of estrogen levels during pregnancy and gray matter volume in the putamen serves as an indicator for this assumption. Further research is needed to investigate whether hormonal alterations temporally precede and potentially cause the observed neural changes, and to delineate mechanisms that link the two changes over time.

Behavioral and brain structural differences were correlated across both groups, as well as within individuals in the control group. Participants with a higher ego-allocentric difference score, indicating a stronger preference for the egocentric strategy, had greater gray matter volumes in the striatal region. Striatal volume was not correlated with neither ego- nor allocentric performance on its own, but was related to the ratio between the two. In our view this finding suggests that structural changes in the striatum are associated with the tendency to use a specific strategy. We also observed group differences in the proportion of hippocampal over striatal volumes that were positively associated correlated with allocentric task performance. These associations are in line with previous findings in human neuroimaging studies, showing that striatal activity and volume correlates with (egocentric) response learning and hippocampal activity and volume with (allocentric) place learning (Bohbot, Lerch, Thorndycraft, Iaria, & Zijdenbos, 2007; Hartley, Maguire, Spiers, & Burgess, 2003; Iaria et al., 2003; Voermans et al., 2004).

The present study has several limitations. First, the cross-sectional, group-comparative design of the present study data does not permit strong causal inferences about the sequence and direction of associations among changes in hormone levels, spatial learning, and structural brain parameters in the course of pregnancy. The directionality of the links between these three sets of variables is unclear; in addition, third variables may exert a common influence on all three. Pregnant women experience a large number of physiological, psychological and environmental changes that potentially exert influence on brain and behavior that are related to spatial learning and memory.

Second, we note that relevant hormonal, structural, and behavioral changes may have taken place during the 55 days elapsing between the prepartal cognitive assessment and the postpartal imaging session. These changes may have influenced the present results in ways that are difficult to predict. The time lag between the cognitive and imaging measurement

also hampered us to find correlations between cognitive and brain structural variables within the peripartal group. For practical reasons, this time lag was unavoidable because ethical considerations prohibited the scheduling of the imaging session during pregnancy. One alternative would have been to shift the cognitive test session closer towards the MRI session, that is, to a time point shortly after birth. However, it is likely that this would have lowered the comparability of the two groups to an even greater extent, as sleep deprivation and distraction due to the likely presence of the baby during testing would have compromised the results.

Third, positive selection bias may have affected the results for the peripartal group. Our sample consisted of women who were able to come to the lab at the very end of pregnancy as well as shortly after delivery. The women in this group may have been positively selected on various dimensions of mental and physical health that are known to relate to the phenomena under study. In fact, this selection bias may help to explain why we do not observe impairments in other cognitive tasks, as observed in previous studies (Henry & Rendell, 2007). While we would agree that this likely bias weakens the external validity of the present results (e.g., generalization to the population of peripartal women), we contend that it improves their internal validity (i.e., studying the effects of estrogen on brain and behavior).

Taken together, our findings demonstrate that pregnancy is associated with decreased striatal volume and altered navigation performance in humans. We observed a lower prevalence of egocentric strategies in spatial learning in pregnant compared to non-pregnant women. We also found a positive association between striatal volume and egocentric strategy prevalence, which is consistent with animal work on hippocampus-based versus striatum-based differences in spatial navigation strategies. Future longitudinal work is needed to better understand the directionality and time course of hormonal, structural, and behavioral changes in the course of human pregnancy.

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Figures

Figure 1. Performance Navigation Strategy Task

Higher performance of control group in Same Direction (SD) Trials (egocentric) (*p* = 0.03); No difference between the groups in Different Direction (DD) Trials (allocentric), group x condition interaction (*p* = 0.03). Error bars represent between-subject standard error (SE). * = significant, p < 0.05

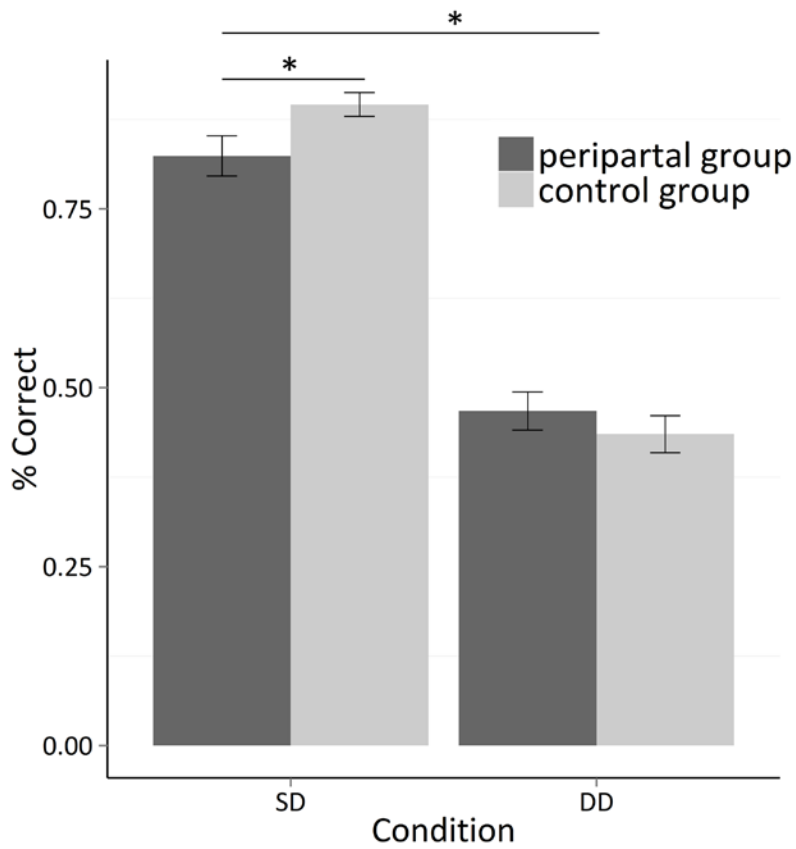

Figure 2. VBM whole-brain comparison of gray matter volume in the peripartal group and control group revealed gray matter decrease in left striatum in the peripartal group (*p*<0.0001, cluster threshold expected voxels per cluster (k>46), corrected for non-stationary smoothness).

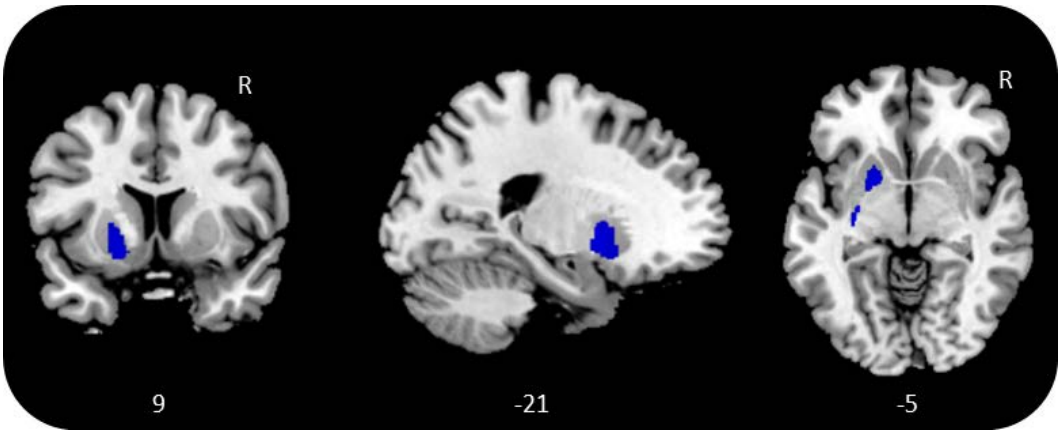

Figure 3. Gray matter (GM) probability in the left putamen (VBM-ROI) correlated with the Navigation Task Difference score ("egocentric prevalence" = Same Direction (SD) - Different Direction (DD)), *r*=0.30, *p*=0.033.

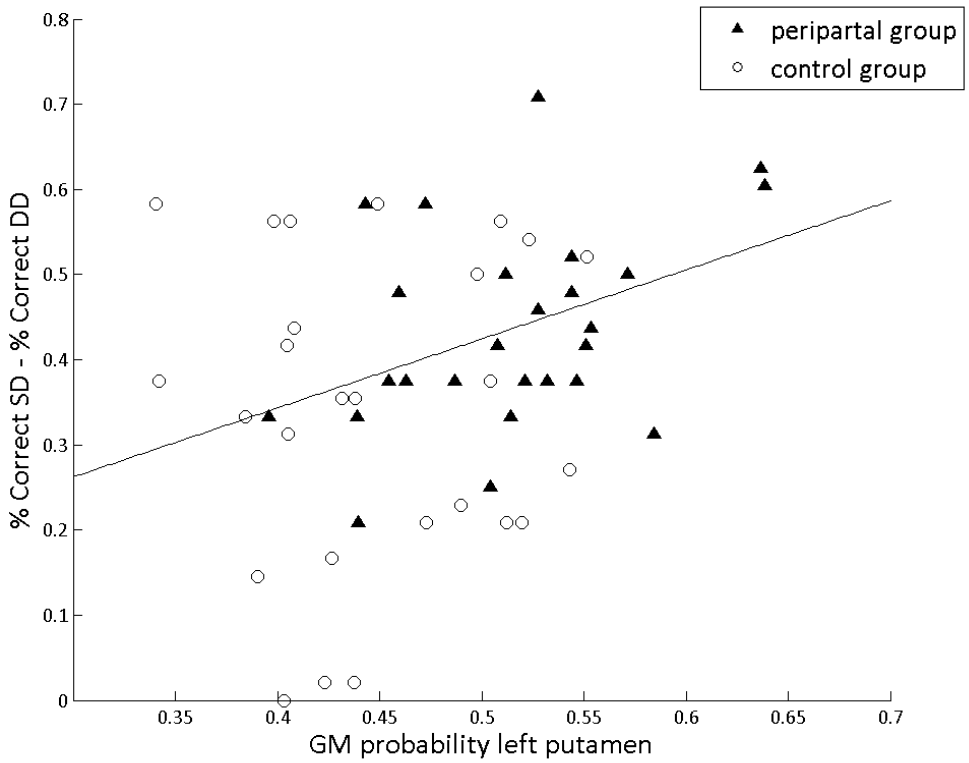

Figure 4. Difference in gray matter (GM) probability between hippocampus and putamen correlated with performance in the Different Direction (DD, allocentric) condition (*r*=0.30, *p*=0.029).