Eur Radiol
DOI 10.1007/s00330-012-2572-5

MAGNETIC RESONANCE

Does the use of hormonal contraceptives cause microstructural changes in cerebral white matter? Preliminary results of a DTI and tractography study

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Received: 28 March 2012 / Revised: 21 May 2012 / Accepted: 24 May 2012

Abstract
Objective To evaluate the effect of monophasic combined oral contraceptive pill (COCP) and menstrual cycle phase in healthy young women on white matter (WM) organization using diffusion tensor imaging (DTI).
Methods Thirty young women were included in the study; 15 women used COCP and 15 women had a natural cycle. All subjects underwent DTI magnetic resonance imaging during the follicular and luteal phase of their cycle, or in different COCP cycle phases. DTI parameters were obtained in different WM structures by performing diffusion tensor fibre tractography. Fractional anisotropy and mean diffusivity were calculated for different WM structures. Hormonal plasma concentrations were measured in peripheral venous blood samples and correlated with the DTI findings.
Results We found a significant difference in mean diffusivity in the fornix between the COCP and the natural cycle group. Mean diffusivity values in the fornix were negatively correlated with luteinizing hormone and estradiol blood concentrations.
Conclusion An important part in the limbic system, the fornix, regulates emotional processes. Differences in diffusion parameters in the fornix may contribute to behavioural alternations related to COCP use. This finding also suggests that the use of oral contraceptives needs to be taken into account when designing DTI group studies.

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Published online: 20 July 2012

Key Points

- *Diffusion tensor MRI offers new insights into brain white matter microstructure.*
- *The effects of oral hormonal contraception were examined in young women.*
- *Diffusion tensor images and hormone blood concentrations were evaluated.*
- *Women using hormonal contraception demonstrated higher mean diffusivity in the fornix.*
- *These changes may contribute to behavioural alternations related to contraception use.*

Keywords Diffusion tensor · Hormonal contraception · Menstrual cycle · Tractography · Fornix

Abbreviations and acronyms

AD	axial diffusivity
CSF	cerebrospinal fluid
COCP	combined oral contraceptive pill
DKI	diffusion kurtosis imaging
DTI	diffusion tensor imaging
EPI	echo planar imaging
FA	fractional anisotropy
FOV	field of view
FSH	follicle-stimulating hormone
GM	grey matter
LH	luteinizing hormone
MD	mean diffusivity
RD	radial diffusivity
ROI	region of interest
SD	standard deviation
VBA	voxel-based analysis
WM	white matter

Introduction

The human menstrual cycle is commonly divided into two phases: the follicular phase, starting at day 1 of menstrual bleeding and ending around day 14 when ovulation takes place, and the luteal phase, which ends at the beginning of the next menstrual bleeding, approximately 14 days later. The clinically most relevant hormones regulating the menstrual cycle are the anterior pituitary produced luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and the ovarian steroids estradiol (E2) and progesterone [1].

Previous studies show that estrogen-sensitive cells show a 2- to 3-fold difference in axosomatic connections during periods of high estrogen plasma concentration [2]. Moreover, a dependency of hormone plasma concentrations on the amount of axosomatic and axodendritic synapses in arcuate nuclei of female rats is reported [3]. An increase of synapses is observed as a decrease in mean diffusivity (MD) [4]. It is our hypothesis that this kind of neuroplasticity can be induced by the hormone level-suppressing effect of combined oral contraception pill (COCP). This effect is most likely to occur in the limbic system and may be linked to behavioural changes.

The menstrual cycle dependency of the female brain has been studied using functional MRI (fMRI) [5–11]. In such a set-up, brain activation patterns are examined as a function of changing hormonal concentrations during the menstrual cycle. Different types of stimuli can be applied, probing the reaction of a woman's brain in different phases of the menstrual cycle. For example, emotional processing is evaluated by measuring the response to words with positive, negative or neutral connotation. Significant effects of cycle phase, as well as correlations of brain activity with estradiol plasma concentrations, are observed. Similar results were obtained by Guapo et al. by showing pictures of emotional facial expressions. Different studies observe a changed response to sexual stimuli in the luteal and follicular phase of the menstrual cycle. Menstrual cycle involvement is also registered using language-, memory-, stress-, and pain-related stimuli [5–11].

The purpose of our work was to evaluate whether diffusion tensor imaging (DTI) can provide additional information regarding white matter microstructural organisation in the female brain. Previous studies report synaptic changes associated with changes in hormone levels in the rat's brain, and functional reorganisation is observed in different menstrual cycle phases [3]. DTI can provide an insight into the microstructural white matter organisation, by measuring water diffusion in different spatial directions. This technique is based on the fact that diffusion magnitude of water molecules is larger along the axonal structures than perpendicular to them. From the diffusion tensor, which provides a mathematical description of the 3D Gaussian diffusion process, rotationally invariant measures can be calculated, describing several diffusion properties. The most frequently used parameters are fractional anisotropy (FA), a normalised measure for the diffusion anisotropy, and mean diffusivity (MD), a measure for the average diffusion magnitude within a voxel [12–15].

DTI has been used to investigate the effect of sex and hormones in puberty on white matter (WM) microstructure [16]. To the best of our knowledge, DTI has not before been used to examine cerebral changes between women using monophasic COCP and women having a natural cycle during their menstrual cycle. The goal of this study was to evaluate the sensitivity of DTI for quantifying such potential differences in WM microstructural properties.

Materials and methods

Subjects

Thirty healthy young women (age range 18–28 years; mean age 21.7±0.5 years), with no previous history of neurological or psychiatric illness, were included in this study. All participants signed a written informed consent, and this study was approved by the local ethics committee. Participants consisted of 15 women using combined (estroprogestogen) monophasic contraception (different formulations were allowed, but subjects using multiphasic or progestogen only pills were excluded), and 15 women with a natural cycle (i.e. no use of hormonal contraception). We acquired diffusion tensor MR images (DTI) during the follicular phase and luteal phase of the menstrual cycle or in the same time window for those on monophasic COCP. The order of MR sessions was counterbalanced across subjects. The naturally cycling women underwent MRI on the 3rd (follicular phase) and the 21st day (luteal phase) of their menstrual cycle. The women taking monophasic COCP underwent MRI on the last day of the pill-free week (considered equivalent to the follicular phase) and the 14th day after starting the next COCP cycle (considered equivalent to the luteal phase). For practical reasons, a variation of 1 day was accepted in both groups. Consequently, a total of 60 DTI data sets were acquired. In addition, we obtained blood samples after each MR examination, in order to measure total venous plasma concentrations of hormones (LH, FSH, progesterone and 17-beta estradiol).

Data acquisition

All DTI data sets were acquired at 3 T (Magneton Trio Tim, Siemens AG, Siemens Medical Solutions, Erlangen, Germany). A 32-channel head coil was used to obtain 40 axial slices using a single-shot echo planar imaging (EPI) sequence. The resulting images had an isotropic resolution of 2.2 mm and a field of view (FOV) of 220×220 mm. Repetition time and echo time of the DTI acquisition were 7,700 ms and 139 ms, respectively. Different diffusion-sensitizing gradients were applied along non-collinear directions: 25 volumes with b=700 s/mm^2 and 40 volumes with b=1,000 s/mm^2 In addition, 10 non-diffusion-weighted images (b=0 s/mm^2) were acquired. The sequence took 14.5 min in total to acquire. We corrected the data sets for subject motion and eddy current induced geometric distortions [17] and a robust non-linear diffusion tensor estimation approach (RESTORE method) was applied [18].

Data analysis

Manual region of interest (ROI) placement was performed by three independent observers using the ExploreDTI toolbox [19]. These ROIs were then used as seed regions for the diffusion tensor tractography algorithm [14] to obtain quantitative DTI information in specific WM fibre bundles. We performed fibre tractography with a deterministic streamline algorithm to reconstruct the pathways of the following WM structures: corpus callosum (genu, body and splenium), cingulum (left and right), fornix and corticospinal tracts (left and right). In order to constrain the streamline tractography results, certain thresholds were defined. Firstly, in order to avoid spurious fibre tracts from entering grey matter (GM) or cerebrospinal fluid (CSF), a threshold for FA of 0.2 was set as the minimal value for fibre tracking to proceed. Secondly an angle exceeding 30° from one voxel to the next was considered a stop criterion to prevent physically non-plausible pathways [20–24].

Mean FA and MD of these reconstructed tracts were statistically analysed in SPSS (http://www.spss.com). Normality of all data was checked with a Kolmogorov–Smirnov test. Since we observed non-normality in some of the data, whenever approptriate, we replaced t-tests or paired t-tests with Mann–Whitney U-tests and Wilcoxon matched pairs signed rank tests to investigate between-group and longitudinal changes, respectively. In addition, we statistically evaluated correlations between hormonal concentrations and diffusion parameters using a Spearman test. For all statistical tests, a P value less than 0.05 was considered significant.

Results

Subjects

Mean subject age was 21.7 (±0.5 standard deviation, SD) years. The mean age for the COCP group was 21.1 (±0.5 SD) years and the mean age for the natural cycle group was 22.3±0.8 years. A t test showed no significant age difference between the two groups (P=0.177).

Hormonal data

Two outliers from the estrogen data in the natural cycle group were removed for all analysis. Hormonal data are depicted in Fig. 1.

Comparing the normally cycling women with the COCP group, we found highly significant differences for all hormones in the luteal phase (P values<0.001), demonstrating the suppressive effect of the pill on pituitary and ovarian secretion. Not unexpectedly, in the follicular phase there were no significant differences, except a borderline difference for progesterone (P=0.004).

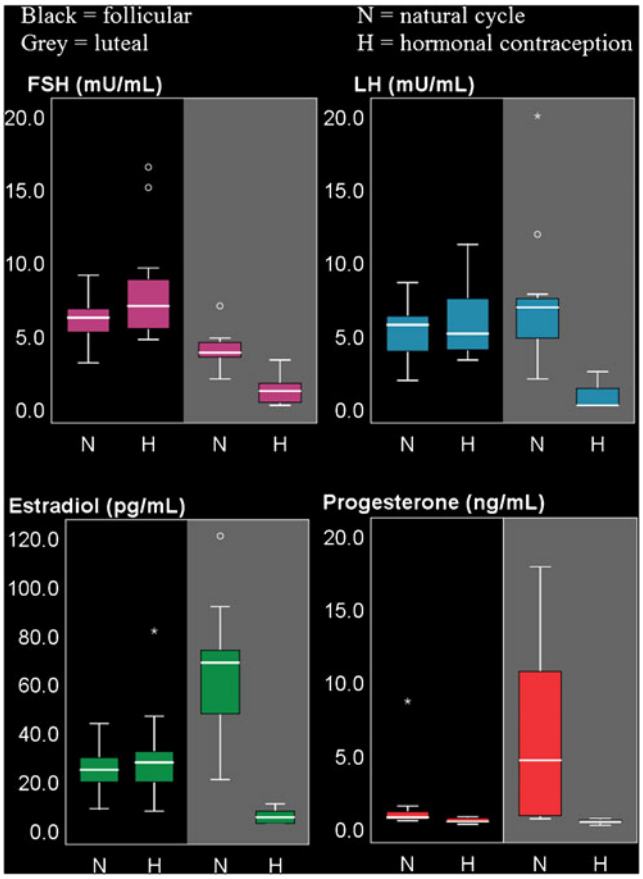

Fig. 1 Box plots of the concentrations of hormones, comparing follicular (*black panel*) and luteal (*grey panel*) phases for the natural cycle group (*N*) and the COCP group (*H*)

Comparing follicular to luteal phase, significant differences in the COCP group for all hormones were found ($P<0.001$ for FSH, LH, estrogen and $P=0.028$ for progesterone) demonstrating the escape from suppression at the end of the pill-free period. In the naturally cycling group the same differences were noted ($P=0.003$ for FSH, $P=0.001$ for estrogen and $P=0.013$ for progesterone), except for LH as the measurement was taken outside the period of the LH peak. All *P* values of the Mann–Whitney *U* tests and Wilcoxon tests are summarised in Table 1.

Table 1 Mann–Whitney *U* test *P* values of all comparisons of the hormonal data

P values		FSH	LH	Estradiol	Progesterone
Natural vs. COCP	Follicular	0.170	0.964	0.525	0.004
	Luteal	<0.001	<0.001	<0.001	<0.001
	Both	0.230	<0.001	<0.001	<0.001
Follicular vs. luteal	COCP	0.001	0.001	0.001	0.030
	Natural	0.010	0.195	0.003	0.023
	Both	<0.001	0.034	0.074	0.388

Tractography

Figure 2 shows the results of observer A regarding the FA and MD of reconstructed WM structures as described above. Among the three independent observers, the fornix was the only WM structure where significant differences in the diffusion parameters were found between both subject groups.

We found a significantly higher MD (*t* test, $P=0.023$) in the fornix for the COCP group compared to the naturally cycling group, when taking both time points together (large effect size: $r=0.749$). This difference was also observed in the follicular phase (*t* test, $P=0.022$, large effect size: $r=0.859$), but not in the follicular phase ($P=0.363$). In spite of the large effect size, differences in MD are not significant enough to withstand a correction made for multiple comparisons (Bonferroni). This is not unexpected or unusual, given the relatively small sample size in our study

Two other observers reproduced the MD differences; one even reported an additional difference between the groups in the follicular phase. We found a high intraclass correlation coefficient (ICC) when comparing the tractography results of the three observers (>0.9).

The fornix was examined in a correlation analysis, using a Spearman test. There were significant correlations of MD with LH ($P=0.015$, correlation coefficient=−0.321) and estradiol ($P=0.014$, correlation coefficient=−0.331) plasma concentrations. Scatter plots are shown in Fig. 3.

Discussion

Apart from their role in procreation, reproductive hormones have a powerful effect on the behaviour of women, as demonstrated by the premenstrual syndrome and late luteal phase dysphoric disorder. Common complaints around the premenstrual phase include physical phenomena and alternations in mood. Moreover, it has been reported that fertile women are more susceptible to symptoms of depression than postmenopausal women and men [25]. Our study evaluates the potential of DTI to quantitatively measure brain WM changes in young women, as a function of the use of monophasic COCP. In a longitudinal set-up, subjects undergo two DTI MR examinations at different time points during the menstrual cycle. Hormone plasma concentrations are simultaneously obtained.

In normally cycling women, the LH and FSH concentrations peak sharply around day 14 of the cycle, initiating ovulation [1]. As a result of the choice of the time points studied in our subjects, this peak is most likely to be missed in the hormonal data. A significant difference in FSH is, however, still observed. Estradiol levels gradually increase during the postmenstrual follicular phase, with a peak level

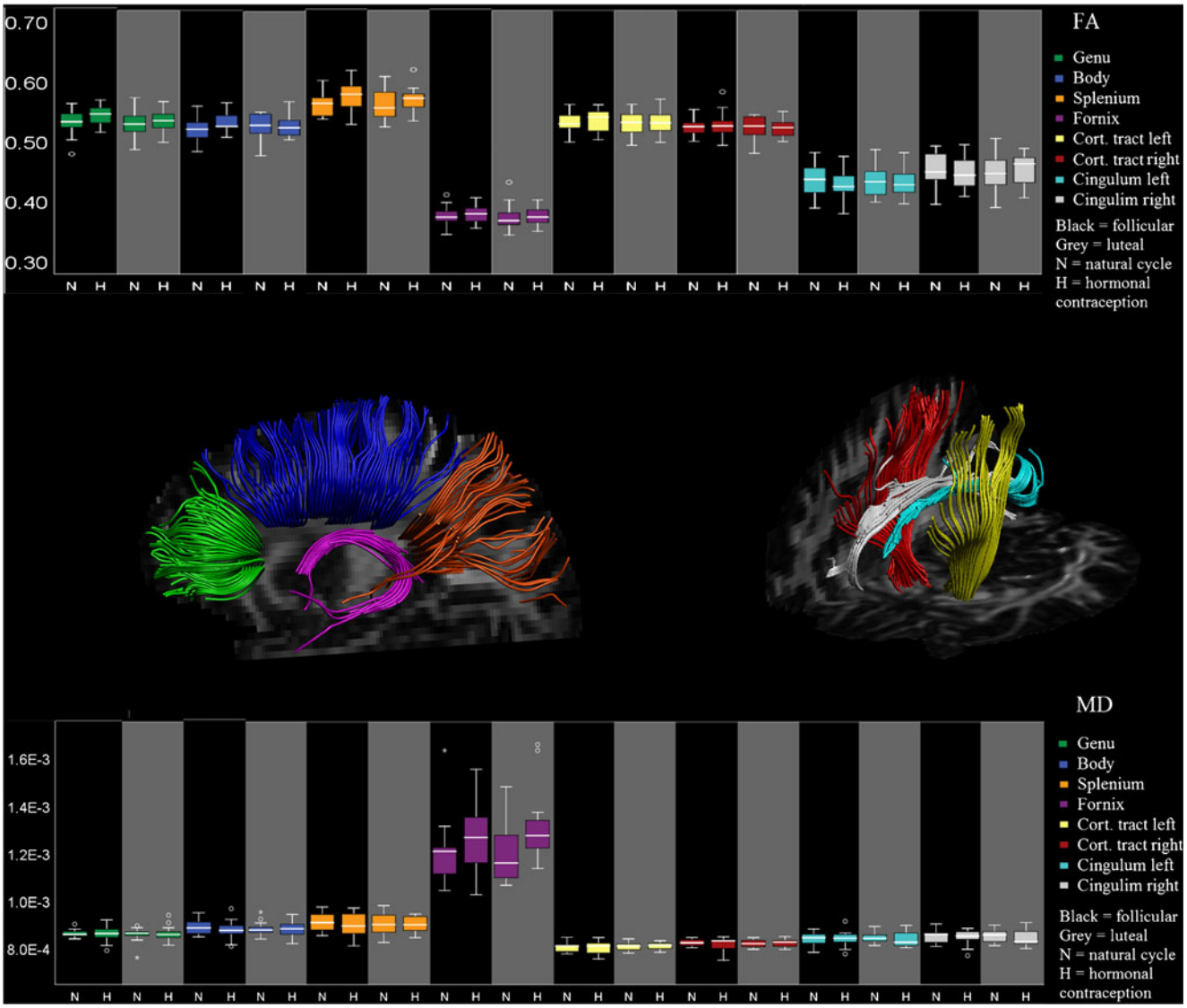

Fig. 2 FA (*upper panel*) and MD (*lower panel*) results from tractography in each white matter structure (colour encoded). Box plots compare follicular phase (*black*) and luteal phase (*grey*) for the natural cycle group (*N*) and the COCP group (*H*)

reached 12–24 h before the LH surge at the ovulation. During the early luteal phase, estradiol levels gradually increase again and peak during mid-luteal phase. Progesterone levels remain low during the follicular phase, and shortly after ovulation, they increase sharply [1]. We indeed observed highly significant differences in estradiol and progesterone levels when comparing follicular and luteal phases in the naturally cycling group. Conversely, when a young woman uses COCP, the plasma hormone levels will show a different pattern. The main mechanism of action of these contraceptives is the inhibition of LH and FSH peaks, preventing ovulation [1]. Plasma concentrations should differ significantly between the naturally cycling group and the COCP group. Our results confirm this hypothesis (Fig. 1 and Table 1). During the pill-free week, these differences fade and we observe only a slight difference in progesterone levels. This is, however, most likely due to one subject with an unusually high progesteron level in the natural cycle group. As is well known when stopping the pill for more than seven consecutive days, this will result in a high percentage of "escape" ovulations. Conversely, during the luteal phase (or after taking the pill for more than 2 weeks), there are large differences in all hormonal levels. This explains the regulating effect of COCP.

Our tractography results show an increased MD of the fornix in the COCP group, especially during the luteal phase. In addition, we found a negative correlation of MD with LH and estrogen plasma concentrations, as shown in Fig. 3. We are well aware of the limitations of the technique used. Caution must be observed when relating diffusion parameters like FA and MD to the biologic microstructural reality. An increase in FA can be the result of increased axial diffusivity (AD, the largest of the tensor eigenvalues), or a decrease in radial

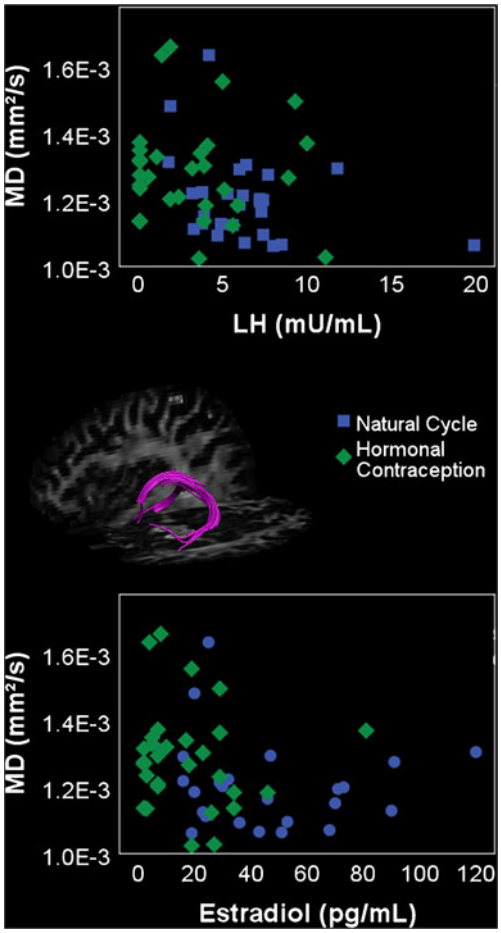

Fig. 3 Scatter plots of the correlation of MD values in the fornix with lutheinizing hormone (*LH*) and estradiol for the natural cycle group (*blue*) and the COCP group (*green*)

diffusivity (RD, average of the two smaller eigenvalues), or a combination of both. Song et al. suggest that an increase in AD reflects an increase in axonal density and that decreased RD indicates degeneration of myelin sheets around the axonal bundles [26]. Although it is tempting to follow this straightforward explanation, there is not much evidence to support this theory, at least not within short time periods [27]. In addition, these microstructural changes can be obscured by macroscopic confounding factors such as crossing fibres and partial volume artefacts [23, 24]. Since the fornix is a relatively small WM tract, adjacent to the ventricles, it is prone to partial volume artefacts [28]. However, we found no significant difference between the number of reconstructed tracts in the fornix between observers nor between subject groups or time points. We therefore believe that, even though partial volume effects may be a source of errors, these inaccuracies are the same for all subjects and do not bias the statistical comparison. As only healthy and young subjects (within a restricted age range) were included in this study, we indeed do not expect large differences in these partial volume effects across the subject groups and over time.

For these reasons, it is not easy to establish an exact link between the effect of menstrual cycle and hormones in the female brain with DTI findings. Previous studies show that short-term alterations in brain microstructure (brain plasticity) can be observed using DTI [4, 20]. An increase in FA and decrease in MD are observed after memory training tasks in rat brains [4] and human brains [20] within a period of 8 weeks. These encouraging results suggest that differences on a slightly smaller timescale, i.e. the menstrual cycle of approximately 4 weeks, can also be feasible.

We only observed differences in the fornix and did not find any changes in the other WM tracts under investigation. The fornix is an important part of the limbic system, regulating emotions, sexual stimuli, etc. These factors are correlated with hormonal levels in previous studies [5–11]. In an fMRI study by Rupp et al. neuronal activity of women in response to pictures of men as potential sexual partners was found to be higher in the luteal phase. The amount of positive reactions is correlated with estradiol and progesterone concentrations. When comparing luteal to follicular phase, activation patterns are different in the medial orbitofrontal cortex [9].

Other studies depict a dependency of hormone levels on the amount of synapses in arcuate nuclei of female rats and find a positive correlation of estrogen plasma concentrations with axosomatic connections in estrogen-sensitive cells [2, 3]. An increase of synapses is observed as a decrease in MD [4]. When comparing these literature data with our own results, the elevated MD in the COCP group might be a consequence of a smaller amount of synapses in the fornix, compared to the naturally cycling group. Especially in the luteal phase, when hormone levels in the normally cycling group indicate a possible recent pregnancy, such a microstructural change in tissue organization of the fornix seems plausible.

If we surmise that the differences we found are linked to the use of COCP, one would expect to find an additional difference within the COCP group when comparing follicular and luteal phases. This was, however, not observed. One possible explanation could be that the contraceptives do not have an effect on the WM microstructure in the time frame of merely 1 week.

All results suggest that there is a difference in the fornix microstructure when comparing both groups. However, further research is needed to corroborate this conclusion. In spite of the high ICC between observers (indicating high reproducibility) there is a variability among the results of our three independent observers, which is due to the user dependency of the manual ROI placement to seed the tractography algorithm [29]. In order to exclude the user dependency of the ROI placement, one can perform a voxel-based analysis (VBA). In VBA, all brain maps are matched to a template by

performing affine and non-linear transformations [30, 31]. It is presumed that every voxel then represents the same anatomical structure, which is in turn also a limitation. In one study investigators compared the ROI and the VBA technique and found comparable results [29]. Because of biological variations, some small structures close to CSF could not be depicted accurately. They concluded that ROI and VBA were able to provide complementary information on the diffusion parameters.

Moreover, the mono-exponential diffusion model in DTI can be extended by changing the probability density function that models the self-diffusion. With the addition of a 4th-order 3D fully symmetric tensor, this technique, known as diffusion kurtosis imaging (DKI), is able to describe the non-Gaussian behaviour. With the use of DKI, one is able to estimate the diffusion parameters more accurately [32].

We purposefully selected our subjects among young women within a narrow age range in order to minimise the influence of age-related differences in diffusional parameters [33, 34]. Given the homogeneity of our population sample, we were able to limit the number of subjects to a total of 30 women. However we are aware that increasing the number of subjects would be beneficial to enhance the statistical power of our study. Therefore our results should be regarded as preliminary. Moreover, the presence or absence of COCP may need to be taken into account in future designs of DTI group studies related to the limbic system in order to minimise the variability of the diffusion metrics.

In the contraceptives group we examined only subjects using the monophasic type of hormonal contraception, i.e. not multiphasic or progestogen-only pills. Different formulations with different amounts of estrogen and progestogen were allowed. The hormonal concentrations in the blood samples did not differ between different formulations, hence we are convinced that this is not a drawback of our study.

In conclusion, we have demonstrated changes of the diffusion tensor parameters in the fornix when comparing women using combined oral contraception to women with a natural menstrual cycle. As an important part of the limbic system, the fornix regulates emotional processes. The physical relationship between DTI measurements and cellular microarchitecture remains under active investigation and is not fully elucidated. Changes in FA and MD values potentially could reflect modifications of the microstructural cellular environment (brain plasticity), changes in the concentrations of intra- and extracellular water within the brain, or a combination of both. It is well known that, in other parts of the body, water retention occurs in the premenstrual phase of the hormonal cycle, though it is unsure whether similar changes occur in the brain. On the other hand, there is evidence that hormone-based brain plasticity can cause changes in microarchitecture of brain tissue within hours [2], and certainly within the time span that separates the luteal from the follicular phase. Further work is needed to discover the underlying biochemical and/or histological basis for the results we observed in our study.

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