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MEETING ABSTRACT

A2.27

Effects of testosterone treatment on hypothalamic microstructure in female-to-male transsexuals

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Background: An increasing number of neuroimaging studies indicates that sex hormones modulate human brain structure and function [1,2]. Recently, we showed that testosterone treatment in female-to-male transsexuals (FtM) elevated the binding of cerebral serotonin transporters, an important protein regulating serotonergic neurotransmission [1]. Furthermore, structural modifications after testosterone treatment were substantiated in gray and white matter using voxel-based morphometry and tractography, respectively (data submitted). As head ganglion of the endocrine system, the hypothalamus plays a key role in hormone function, with its structure and cell assembly being shaped by steroid hormones [3,4]. Here, our aim was to closer examine microstructural neuroplastic changes in the hypothalamus by investigating the effect of hormone treatment on gray matter microstructure in FtM transsexuals using diffusion tensor imaging (DTI).

Methods: Twenty-three FtM transsexuals were included in this longitudinal study (age: 27.3 ± 6.3; mean ± SD). Transsexuals were measured before start of treatment, after 4 weeks, and after about 4 months of treatment start. Treatment consisted of 1000 mg testosterone undecanoate every 12 weeks and in two cases additionally 10 mg lynestrenol daily. Transsexuals were scanned on a 3 T Tim Trio Scanner (Siemens Medical, Germany). DTI acquisition was performed with an isotropic resolution of 1.6 mm^3 acquiring diffusion-weighted images in 30 directions with a *b* value of 800 s/mm^2. Calculation of mean diffusivity (MD) maps was done in FSL [5] after eddy current correction. Spatial normalization of MD maps was carried out with deformation fields obtained from segmentation of baseline T1-weighted images with the VBM8 toolbox. Repeated-measures ANOVA and post-hoc pairwise comparisons were done using SPM. Correlations between changes in MD and changes in bioavailable testosterone plasma levels were calculated. The statistical threshold was set at $p < 0.05$ FDR cluster-corrected.

Results: Results: DTI analysis of whole brain gray matter revealed significant differences in MD maps between the three time points in bilateral posterior hypothalamus (x = 6, y = −7, z = −15, F = 10.3; and x = −4, y = −7, z = −15, F = 10.2), as well as in left fusiform and middle temporal gyrus (k ≥ 47 cluster size, corresponding to expected voxels per cluster of k = 47, ANOVA, $p < 0.001$ uncorrected). Post-hoc pairwise comparisons revealed significant MD reductions in bilateral posterior hypothalamus (x = 6, y = −7, z = −17, T = 4.0; and x = −4, y = −7, z = −15, T = 4.3) after 4 weeks of treatment ($p = 0.046$, corrected), and a more pronounced reduction after four months of treatment (x = 9, y = −6, z = −8, T = 4.78; and x = −7, y = −7, z = −13; T = 3.63; $p < 0.001$, corrected). After four months of treatment, correlation analysis revealed a significant negative association between MD changes in the right hypothalamus (x = 9, y = −6, z = −8; *i.e.* peak voxel of the post-hoc *t*-test) and increases in bioavailable testosterone ($r = -0.64$; $p = 0.017$).

Discussion: Our results indicate that testosterone treatment leads to microstructural changes in hypothalamic tissue of FtM transsexuals. Several post-mortem studies have indicated that pre- and perinatal testosterone surges in the womb shape hypothalamic nuclei. These processes were proposed to underlie a person's gender identity [3,4]. Here, we propose that also changes in adult testosterone levels affect hypothalamic microstructure. Microstructural changes in hypothalamic nuclei, as seen in our study, may reflect adaptive changes in endocrine function after prolonged exogenous administration of testosterone in FtM transsexuals.

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