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Neuronal plasticity of language-related brain regions induced by long-term testosterone treatment

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INTRODUCTION

The sex steroid hormone testosterone exhibits a substantial influence on behavior and cognition via the modulation of underlying brain structures and function. Testosterone plays a particular role in language function, showing associations with vocabulary and sexually dimorphic gray matter regions [1]. However, the majority of studies are limited to cross-sectional investigations or single hormone applications due to ethical reasons. Here, we assessed the influence of continuous high-dose testosterone treatment on brain structure and function in female-to-male (FtM) transsexuals before and after start of hormone therapy.

METHODS

Eighteen FtM subjects (27.3±6.4 years) underwent 3 and 7 Tesla magnetic resonance imaging (MRI) before and after four weeks of testosterone treatment (1000mg/12 weeks intramuscular or 50g/day transdermal). Blood samples were taken at each MRI session to identify associations between bioavailable testosterone (Tbio) and imaging parameters. First, gray matter volume was assessed by segmentation of T1-weighted structural images (MPRAGE, 1.1x1x1mm) using voxel-based morphometry. Second, white matter fiber tracts were reconstructed from diffusion weighted images (1.64mm isotropic, 30 directions, b-value=800s/mm^2) with probabilistic tractography. Diffusivity metrics were then averaged along the entire tracts. Third, functional connectivity was computed from resting-state functional MRI (7T Tesla EPI, 1.5x1.5x3mm). Preprocessing of functional connectivity data included band-pass filtering and removal of motion parameters, white matter and ventricular signal but not the global signal. Significant clusters from the gray matter analysis were used as seed regions for tractography and functional connectivity. Regression analysis was carried out to evaluate relationships between changes in Tbio and changes in imaging parameters between the two MRI scans.

RESULTS

We observed negative associations between differences in Tbio and differences in gray matter volume within the left inferior frontal gyrus (Broca's area, r=-0.88) and the left superior temporal gyrus (Wernicke's areas, r=-0.87, both $p<0.05$ whole brain FWE-corrected). Accordingly, changes in Tbio predicted changes in mean diffusivity of the extreme capsule pathway (rho=-0.63, $p<0.005$) but not the arcuate fasciculus. Finally, functional connectivity between the above identified gray matter regions increased with increasing levels of Tbio (rho=0.55, $p<0.01$). None of these results changed when correcting for baseline Tbio, baseline imaging parameters or age.

CONCLUSIONS

In line with previous observations of neuronal plasticity [1], decreases in gray matter volume of Broca's and Wernicke's areas may be related to attenuated language performance in men [2]. On the other hand, reductions in white matter mean diffusivity have been demonstrated to reflect increases in myelin formation [3]. This indicates a strengthening of the corresponding fiber tract, which is involved in semantic processing and language comprehension [4]. The enhanced structural connection is further supported by the increased functional connectivity between Broca's and Wernicke's areas. Taken together, it seems that testosterone exhibits differential effects on neuronal plasticity in language-specific regions of the adult human brain. Although

increases in structural and functional connectivity may compensate deteriorations in gray matter volume, the latter effect appears to be more important for cognitive function, since language performance is decreased in men [2] and androgen-treated FtM [5].

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DISCLOSURE

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