Background: Converging evidence indicates that sex steroid hormones influence brain function and structure. Several studies show the strong influence of sex steroid hormones on neuronal response to emotional and cognitive demanding stimuli. Recent studies also indicate sex steroid hormones to influence brain structure and connectivity. The ultrahigh-field MRI study proposed gives us the unique opportunity to measure changes in brain function and structure induced by long-term opposite-sex steroid hormone administration.

Objectives of the study: 1. to prove the influence of high-dose, long-term opposite-sex steroid hormone treatment on functional brain response in transsexuals. 2. to investigate the influence of hormone treatment on resting state functional connectivity and brain morphology. 3. to investigate differences between transsexuals and healthy control subjects in brain function and functional connectivity, brain morphology and structural connectivity.

Study design: Single-blind, longitudinal study. Transsexuals and healthy control subjects will undergo three 7 Tesla ultrahigh-field MRI scan sessions: 1. baseline (before hormone treatment), 2. after 4 weeks of treatment and 3. after 4 months of treatment. We propose an overall study duration of 36 months.

Materials and Methods: Functional and structural MRI measurements will be performed on a 7 Tesla scanner providing high sensitivity data with high spatial and temporal resolution. Each subject will perform six different fMRI paradigms: (I-III) three emotion paradigms; (IV-V) two cognitive paradigms and (VI) a motor paradigm. Furthermore, we will assess resting-state functional connectivity and use diffusion tensor imaging (DTI) to obtain anatomical connectivity measures. Structural data will be examined using voxel-based morphometry (VBM) and region of interest based morphometry.

Study population: 20 healthy female-to-male (FtM), 20 healthy male-to-female (MtF) transsexuals (aged 18-50), free of hormone-medication at baseline; 40 healthy controls, matched for sex, age and sexual orientation.

Relevance and implications of the study: This will be the first imaging study to investigate the effects of high-dose, long-term opposite-sex hormones on task-specific brain activation in both sexes using 7 Tesla ultrahigh-field MRI. This study will also be the first to investigate differences between healthy controls and transsexuals and the influence of opposite-sex hormones on resting state functional connectivity, diffusion weighted connectivity and on whole-brain morphology using VBM. The results of this study will provide essential data for improved understanding of neural sex differences associated with differences in hormonal states in humans. In addition, this study will shed new light on sexual differentiation of the brain in transsexuals that possibly contrasts with that of the genetic and physical characteristics of sex.