Social norm processing as an endophenotype of social anxiety disorder: a family study in two generations

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The combination of high-resolution PET and structural MRI with novel quantification methods allows for generation of population based brain atlases showing these molecular brain targets in great detail. In vivo mapping of those systems in the human brain provides exciting opportunities for exploring these in relation to, e. g., brain disorders or in experimental medicine studies of pharmacological interventions. One such example of relevance for the 5-HT system is a study where healthy volunteers underwent three-week intervention with either placebo or the selective serotonin reuptake inhibitor (SSRI) fluoxetine and were scanned before and after with fMRI and the 5-HT4 receptor radioligand [11C] SB207145 PET. The intervention did not result in any significant group-differences in emotional face processing with fMRI. Only when taking the SSRI intervention associated changes in central 5-HT levels, as measured with the 5-HT4 receptor radioligand [11C]SB207145 PET, into account an interesting observation emerged: The greater the increase in central 5-HT levels, the lower the threat-related amygdala reactivity [7]. This provides direct evidence that individual changes in brain 5-HT levels are linked to threat-related amygdala reactivity.

In conclusion, whereas several fMRI studies identify amygdala, medial and dorsolateral prefrontal cortex and subgenual cortex/anterior cingulate as key structures, PET neuroimaging studies of 5-HTT binding suggest that dorsolateral prefrontal cortex, anterior cingulate and the raphe regions are specifically involved. The separate methodological challenges associated with these two non-invasive imaging modalities will be discussed.

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Posters

P.3.001 **Social norm processing as an endophenotype of social anxiety disorder: a family study in two generations**

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Background and purpose: Endophenotypes are measurable characteristics related to complex psychiatric disorders and reflective of genetically-based disease mechanisms. They are associated with the disorder, heritable, and co-segregate with the disorder within families of probands [1]. A core aspect of Social Anxiety Disorder (SAD) is the fear of being negatively evaluated in social situations. This fear relates to disturbances in self-referential processing, which have been linked to increased brain activation in the amygdala and medial prefrontal cortex (MPFC) [2]. A study using a Social Norm Processing Task (SNPT) showed increased responsiveness of the MPFC in response to unintentional transgressions of social norms in SAD-patients [3]. However, little is known about these processes in family-members of SAD-patients, who have an increased risk of developing the disorder [4].

Here, we used an adapted, Dutch version of the SNPT (D-SNPT) to investigate behavioral ratings and neural responses related to stories describing social events, in a unique sample of SAD-patients and their family-members of two generations. We tested the assumption that altered social norm processing co-segregates with social anxiety within these families.

Methods: Nine families with a genetic predisposition for SAD participated in this study. Families contained at least two SAD-cases and were selected based on the combination of a SAD-patient with a child with (elevated levels of) social anxiety. Family-members of two generations were included (total sample n = 114, 56 males, mean age 31.4 y, range 8.9–61.5 y), and the number of social anxiety symptoms was determined using an age-appropriate questionnaire. Functional MRI data were acquired during the D-SNPT. In this paradigm, participants read stories describing neutral social events ("neutral condition"), events in which social norms were unintentionally transgressed ("unintentional condition") and events in which social norms were intentionally violated ("intentional condition"). Stories were written in second person ("You") and participants were asked to imagine themselves in the situations described. After the scan session, participants rated the stories on embarrassment and inappropriateness. Analyses focused on differences in brain activation within the MPFC and were performed using FSL-FEAT.

Results: There was a significant effect of condition on the ratings of embarrassment (F2,226 = 1109.3, p < 0.001) and inappropriateness (F2,226 = 1406.5, p < 0.001): participants rated the intentional stories as the most embarrassing and most inappropriate. Number of SA-symptoms was positively correlated with reported embarrassment in all conditions (neutral: p < 0.001; unintentional: p = 0.003; intentional: p = 0.005; all correlations corrected for age, gender and family-structure), but not with the reported inappropriateness. Reading the stories evoked activation within the MPFC in all conditions (whole-brain cluster-corrected, p < 0.05). The severity of SA-symptoms was positively correlated with activation within the left MPFC in both the intentional and unintentional condition (contrast intentional condition>baseline; small-volume corrected, p < 0.05; contrast unintentional condition>baseline, small-volume corrected, p < 0.05), but not within the neutral condition.

Conclusions: The results of this study confirm that aberrant social norm processing co-segregates with social anxiety within families enriched for SAD. Thereby, social norm processing is a promising endophenotype for SAD. Future research needs to establish the heritability of social norm processing.

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P.3.002 **Effects of fludrocortisone administration on cognitive functions in depressed and in healthy subjects**

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Background: People suffering from major depression often show impaired cognitive functions while cortisol secretion is increased. Most pronounced impairments affect memory, attention and executive functions. Being predominantly expressed in the hippocampus and prefrontal cortex, mineralocorticoid receptors (MRs) are linked to cognitive functions and cortisol inhibition. Therefore, we investigated whether administration of fludrocortisone, a potent MR-agonist, (1) improves cognitive functions and (2) decreases cortisol levels in participants with major depression and healthy controls [1,2].

Methods: In this randomized, double-blind, within-subject, cross-over study design, twenty-four drug-free depressed patients and twenty-four age-, sex- and education-matched healthy controls were treated with either 0.4 mg fludrocortisone or placebo. Cognitive functions were assessed between 2:00 and 5:00 pm; cortisol secretion was measured during cognitive testing using saliva samples.