

processes in both healthy and clinical populations, including the study of anxiety disorders and their treatment.

**Keywords:** Fear Extinction, fMRI, Anxiety Disorders, ventromedial prefrontal cortex, Anterior Cingulate Cortex

### 15. Respiratory Sinus Arrhythmia and Ventromedial Prefrontal Function in Veterans with Posttraumatic Stress Symptoms

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**Background:** Adaptive emotional responding requires flexible regulatory control of autonomic response systems, thought to involve the ventromedial prefrontal cortex (vmPFC). Individuals with posttraumatic stress disorder (PTSD) show compromised vmPFC function and parasympathetic tone—as reflected by reduced respiratory sinus arrhythmia (RSA)—yet previous studies have not drawn a direct link between these deficits.

**Methods:** We conducted fMRI scanning during an unpredictable threat anticipation task in 51 male veterans with a broad range of PTSD symptoms. We calculated RSA during a separate resting scan, and conducted voxelwise regression analysis across the medial prefrontal cortex to identify associations between resting RSA and task-related anticipatory threat activation.

**Results:** Replicating and extending previous findings, re-experiencing symptoms of PTSD were inversely correlated with resting RSA ( $r = -0.37$ ,  $p < 0.05$ ). Re-experiencing symptoms were also associated with relatively undifferentiated vmPFC activation across conditions of safety and threat ( $p < 0.05$ , small-volume corrected). Directly linking these two findings, we identified a novel relationship between resting RSA and vmPFC activation: veterans with reduced RSA showed less differentiated responses across conditions of safety and threat in an anatomically overlapping aspect of the vmPFC ( $p < 0.05$ , small-volume corrected).

**Conclusions:** The present data tie together reduced resting RSA, undifferentiated vmPFC activation, and elevated re-experiencing symptoms in combat veterans. These findings provide a theoretically parsimonious account in which intrusive trauma symptoms are associated with reduced neural control over flexible autonomic responding. More broadly, these data underscore the importance of considering individual differences in discrete symptom clusters when investigating neurobiological mechanisms of PTSD.

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**Keywords:** PTSD - Posttraumatic Stress Disorder, ventromedial prefrontal cortex, Respiratory Sinus Arrhythmia, Veterans, Parasympathetic Arousal

### 16. Sample Size Matters: A Voxel-Based Morphometry Multi-Center Mega-Analysis of Gray Matter Volume in Social Anxiety Disorder

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**Background:** Social Anxiety Disorder (SAD) is a disabling psychiatric disorder, associated with high co-morbidity. Previous research on structural brain alterations associated with SAD has yielded inconsistent results concerning changes in gray matter (GM) in various brain regions, as well as on the relationship between GM and SAD-symptomatology. These heterogeneous findings are possibly due to limited sample sizes. Multi-site imaging offers new possibilities to investigate SAD-related GM changes in larger samples.

**Methods:** An international multi-center mega-analysis on the largest database of SAD brain scans to date was performed to compare GM volumes of SAD-patients ( $n=174$ ) and healthy participants ( $n=213$ ) using voxel-based morphometry. A hypothesis-driven region of interest (ROI) approach was used, focusing on the basal ganglia, amygdala-hippocampal complex, prefrontal cortex and parietal cortex.

**Results:** SAD-patients had larger GM volume in the dorsal striatum when compared to healthy participants. This increase correlated positively with the level of social anxiety symptoms. No SAD-related differences in GM volume were present in the other ROIs.

**Conclusions:** The results suggest a role for the dorsal striatum in SAD, but previously reported SAD-related changes in GM in the amygdala, hippocampus, precuneus, prefrontal cortex and parietal regions were not replicated. Thereby, our findings indicate that sample size matters and stress the need for meta-analyses like those performed by the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) Consortium and its working groups. Actually, the collaborative effort for this work has resulted in the start of the ENIGMA-Anxiety workgroup.

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**Keywords:** Social Anxiety Disorder, Voxel Based Morphometry

### 17. Emotional Processing in OCD - A Meta-Analysis of 23 Functional Neuroimaging Studies

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**Background:** Dysfunctional emotional processing of intrusive thoughts, images and impulses is an important aspect of obsessive-compulsive disorder (OCD). Different designs have been used to study emotional processing in OCD, including symptom provocation and cognitive paradigms using emotional stimuli. However, studies show considerable variability in findings, methodology, and patient characteristics.

**Methods:** 23 functional neuroimaging studies comparing OCD patients and healthy controls using fMRI or PET were analyzed using seed-based *d* mapping. We performed a main meta-analysis comparing patients and healthy controls, and meta-regressions of medication usage, stimulus duration, symptom severity using Y-BOCS, and comorbidity. Jackknife and publication bias analyses were also performed.

**Results:** OCD patients, compared with healthy controls, show increased activity in the bilateral amygdala, right putamen, orbitofrontal, middle temporal, and left inferior occipital cortex during emotional processing. Right amygdala hyperactivity was most pronounced in unmedicated patients and in studies with short stimulus durations. Symptom severity was related to increased activity in the orbitofrontal, anterior cingulate cortex and precuneus. Comorbid anxiety disorders were associated with more right amygdala and putamen activity, while comorbid mood disorders were associated with more activity in the right insula and cerebellum. Comorbidity in general predicted decreased activity in the left amygdala. Jackknife analysis showed that activity in the inferior prefrontal cortex in patients and dorsomedial prefrontal cortex in controls were possibly underestimated. There was no evidence of publication bias.

**Conclusions:** OCD patients show increased emotional processing related activity in limbic, frontal and temporal regions. Both methodology and patient characteristics likely influence neuroimaging findings, especially regarding the amygdala activity.

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**Keywords:** Obsessive Compulsive Disorder (OCD), Neuroimaging, Meta-analysis, Amygdala, Anxiety

### 18. In Vivo Quantification of mGluR5 Availability in Posttraumatic Stress Disorder

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**Background:** Posttraumatic stress disorder (PTSD) is associated with considerable emotional, financial, and social burden (McCrone et al., 2003) and heightened risk for suicide (Ramsawh et al., 2014). Yet, relatively little is known about the pathophysiology of PTSD on a molecular level. The metabotropic glutamatergic receptor (mGluR5) is implicated in animal models of fear extinction (Fontanez-Nuin, et al., 2011) and may contribute to the pathophysiology of PTSD. This study examined the relationship between mGluR5 availability and suicidality in vivo in PTSD.

**Methods:** Sixteen individuals with PTSD and 16 age-, sex-, and smoking-matched healthy controls participated in an [18F]FPEB PET scan and comprehensive clinical assessment. Volume of distribution (VT: ratio of activity in tissue relative to that in blood) in grey matter regions was computed.

**Results:** We observed significantly greater mGluR5 availability in individuals with PTSD compared to controls in brain regions implicated in the neurobiology of PTSD [dorsolateral PFC (dlPFC; 19% higher; Cohen's *d*=0.92); ventromedial PFC (vmPFC; 18% higher; Cohen's *d*=0.88), and orbitofrontal cortex (OFC; 18% higher; Cohen's *d*=0.88). Higher mGluR5 availability was associated with greater PTSD symptom severity (*p*<.04) and presence of suicidal ideation on scan day (*p*<.05).

**Conclusions:** This is the first in vivo investigation implicating mGluR5 dysregulation in PTSD, which be indicative of lower glutamate levels or dysregulation in the glucocorticoid system. Importantly, higher mGluR5 availability was associated with increased PTSD symptom severity and presence of suicidal ideation. Our findings suggest a potentially crucial role for mGluR5 in the pathophysiology and suicide risk in PTSD.

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**Keywords:** PTSD, glutamate, PET, suicide, imaging

### 19. Amygdala Subnuclei Volumes Differ among PTSD, Asymptomatic Trauma-Exposed and Healthy Individuals

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**Background:** The clinical consequences of trauma differ across individuals: while some develop post-traumatic stress disorder (PTSD), others may not present with significant psychopathology. A growing body of evidence is pointing to the anatomical and physiological properties of the fear conditioning circuitry, and the amygdala in particular, as the substrate that explains different trauma-related clinical