Decreased functional connectivity between posterior insula and amygdalar-hippocampal complex in major depression associated with uncertainty of a negative event

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Background: Alterations in negative valence systems are core pathophysiological components of major depressive disorder (MDD). Negativity biases are detectable in amygdala and striatal networks upon discrimination of facial emotions [1], yet less is known about neuronal network alterations in MDD associated with negative valenced events such as pain. Hence, we conducted a fMRI experiment with MDD patients and calculated resting-state functional connectivity in a pain paradigm.

Methods 33 unmedicated MDD patients (mean age±SD=31.0±9.1 years, 23 women, mean HAMD=26.4) with a current episode and 37 healthy subjects (HC, 26.5±6.6, 22w) underwent 7T task and resting-state (excluding 2 MDD patients) fMRI. Acquisition parameters were: multiband sequence (multiband factor 3) with TE/TR=23/1400ms, voxel size=1.5×1.5×1mm, 0.25mm gap, 78 slices. Visual cues indicated painful or non-painful stimulation. An unsure condition signalled a 50:50 chance of painful or non-painful stimulation. Preprocessing was performed in SPM12 including slice-timing correction, realignment (mean image), spatial normalization and smoothing with 8mm FWHM. Resting-state data were band-pass filtered (0.009<f<0.08Hz) and cleared of potentially confounding signals (head motion, white matter and ventricular signal; also filtered). Expected stimulation (both painful and non-painful) was contrasted against unsure stimulation. A full factorial model was calculated in SPM12, adjusting for sex, age, and difference in stimulation and pain threshold applying the cluster-level family-wise error rate (FWE) correction at p<0.05.

Results: Expected stimulation vs. uncertain stimulation lead to increased right posterior insular activation (t=4.5, x,y,z=32, -12, 10, pFWE,cluster<0.01) in MDD patients compared to healthy controls. Decreased rsFC was observed in MDD patients between the right dorsal insula (seed) and the bilateral hippocampal head and basolateral amygdala (left t=4.76, x,y,z=-18, -6, -12, pFWE,peak<0.05; right t=4.08, x,y,z=18, -6, -14, puncorr,peak.<0.001) in expected stimulation vs. uncertain stimulation.

Conclusions: In MDD patients, insular dysfunction was observed associated with decreased interoceptive activity [2] and amygdala dysfunction with altered emotional regulation [3]. Here, with task-based and resting-state fMRI we demonstrate that uncertainty of a negative event is associated with increased insular activation, which is further linked to decreased hippocampal-amygdalar coupling. This result underlines impairments of neuronal networks mediating evaluation of somatic and emotional states in MDD.