The effect of paroxetine on amygdala reactivity after emotional faces measured with fMRI

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BACKGROUND

• Selective Serotonin Reuptake Inhibitors (SSRIs) are frequently used for Major Depressive Disorder (MDD)
• SSRIs decrease reactivity of the amygdala to negative facial expressions measured with functional Magnetic Resonance Imaging (fMRI)
• Previous studies could not distinguish whether SSRI-effects or clinical improvement changed amygdala reactivity. Placebo-control was considered unethical
• Placebo-controlled dose-escalation in initial nonresponders may identify specific SSRI-effects

AIMS

• To compare amygdala reactivity after negative emotional faces in MDD patients vs. healthy controls (HC)
• To quantify changes in amygdala reactivity over time during treatment of MDD with paroxetine
• To quantify changes in amygdala reactivity in paroxetine responders vs. non-responders
• To quantify the effects of dose-escalation of paroxetine

METHODS

• Inclusion:
  - 22 SCID diagnosed MDD patients (M+F, age 43.4 ±7.9 yrs, Hamilton [HDRS] score >18, drug-naïve or drug-free for ≥ 4 weeks)
  - 22 age- and sex-matched HC (43.7 ±8.0 yrs, without lifetime mental disorder)
• Exclusion:
  - patients with bipolar or psychotic disorders.
  - HC with psychiatrically affected 1st degree relatives
• Treatment of patients:
  - paroxetine 20mg/day (6 weeks)
  - non-responders (< 50% ↓ HDRS after 6 weeks; n= 12) were randomized (T0) to double blind DE or placebo for 6 more weeks (T1)
(Figure 1)
• 3 fMRI sessions (3D structural & T2 BOLD contrasts):
  - at baseline, T0 and T1
  - affective facial expression paradigm comparing angry+anxious (negative) faces versus blurred faces
  - 3T Phillips Intera MRI; 6-channel headcoil; fMRI-settings: TE/TR= 35/25 ±0.4 ms., flip angle=90°, matrix=128×128, 36 ascending slices, slice thickness= 3 mm, interslice gap = 0.3 mm, scan time=10 min., standard individual preprocessing
• Planned contrasts: Baseline scans:
  - MDD vs. HC, groupwise changes over time (Bsl-T1), T0/T1 responders vs. non-responders, dose-escalation vs. paroxetine 20mg/day

RESULTS

• Analyzable scans: 21 patients and 21 HC at baseline, 18 T0 and 17 T1 during follow-up
• 12 non-responders were randomized (5 true DE). At endpoint (T1) 11/18 patients responded
• Baseline: Patients had higher activity in left insula, right amygdala (Fig. 2), while HC had higher activity in right DLPFC, left DMPFC, bilateral fusiform face areas and left cerebellum (z>3.09)
• Endpoint: Patients had higher activity in bilateral DLPFC, right dorsal anterior cingulate and left putamen compared to baseline. Mean amygdala activity did not decrease significantly at T1
• Response: Non-response was associated with higher bilateral amygdala activity (and right insula and OFC) compared with responders (T0 & T1 scans combined; z>3.09; Fig 3).
• Dose-escalation: At endpoint DE (46 ±8.9mg/day; n= 5) resulted in higher activity in right hippocampus compared to paroxetine 20mg/day (n= 12; z>3.09; Fig 4). Amygdala reactivity did not significantly differ

CONCLUSIONS

• In depressed patients amygdala reactivity for negative emotional faces is increased
• Amygdala reactivity to negative emotional faces decreases when MDD severity is diminished
• The reduction in amygdala reactivity is not a direct pharmacological effect, but is probably associated with increased control by dorsal cortical (cognitive) networks