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

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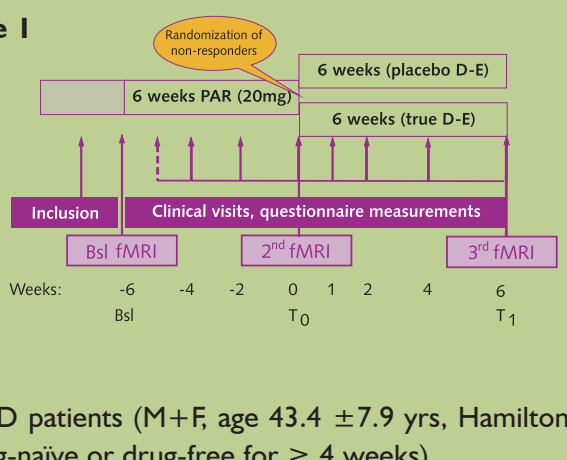
BACKGROUND

- 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

Figure 1



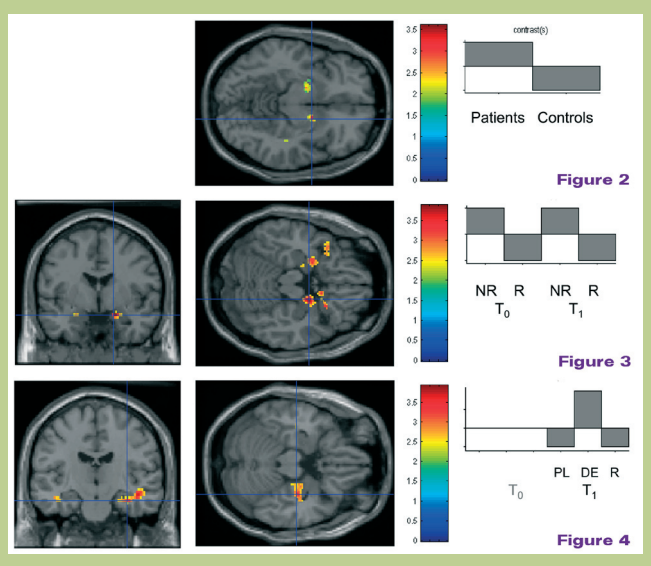
METHODS

- 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 faces4
  - 3T Phillips Intera MRI; 6-channel headcoil; fMRI-settings: TE/TR= 35/2530.4 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

Figure 2. Right amygdala activity in patients (n= 21) versus controls (n=21).
Patients > controls, masked for patients. Crosshair at x= 18, y= 2, z= -9 (MNI).

Figure 3. Bilateral amygdala activity in depressed non-responders to paroxetine20-50mg/day. Full-factorial model. Non-response > response, masked for non-responders. Crosshair at x= 18, y= -2, z= -18 (MNI).

Figure 4. Increased activity in right hippocampus after dose-escalation of paroxetine. Full-factorial model. True DE > Placebo DE + Non-randomized, masked for true DE. Crosshair at x= 34, y= -16, z= -21 (MNI).



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

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