Association between neural correlates of fear conditioning and therapy response in patients with panic disorder and agoraphobia

U. Lueken1,2, H.-U. Wittchen1,2, C. Konrad3, B. Straube2, A. Wittmann4, A. Ströhle4, B. Pfeifer5, E. Aerts5, L. Reinhardt6 & T. Kircher3

1Institute of Clinical Psychology and Psychotherapy, Technische Universität Dresden, Dresden (Germany) ; 2Neuromaging Center, Dept. of Psychology, Technische Universität Dresden, Dresden (Germany); 3Department of Psychiatry and Psychotherapy, Universitätsklinikum Hamburg-Eppendorf, Hamburg (Germany); 4Department of Psychiatry and Psychotherapy, Clinic for General Internal Medicine, Charité, Universitätsmedizin Berlin, Berlin (Germany); 5University hospital Münster, Department of Clinical Radiology, Münster (Germany); 6Department of Psychiatry and Psychotherapy, WWZ Klinikum Aachen, Aachen (Germany)

Background

- Panic disorder with agoraphobia (PD/AG) is a common and debilitating anxiety disorder characterized by recurrent and sudden attacks of intense anxiety and concerns about their potential implications1.
- Fear conditioning and extinction may represent a pathognomonic pathway for the development and treatment of PD/AG. Neural correlates of fear conditioning could therefore provide an experimental approach to investigate treatment response in PD/AG.

Behavioral studies on differential fear conditioning further suggest a failure to inhibit fear reactions in the presence of safety signals in PD/AG2,4.

Research question:

- Do treatment responders and non-responders differ in neural correlates of fear conditioning already prior to treatment?

Methods

Sample

- Within the national research network PANIC-NET, n = 369 patients were treated with a manualized CBT focussing on exposure in situ. Eighty-nine patients also participated in the fMRI study. Valid data sets from n = 49 patients were used for the present analysis.

Treatment response: >50% reduction in Ham-A scores baseline to post assessment. Responders (R) and non-responders (NR) were comparable in baseline characteristics (Table 1).

Differential fear conditioning task

Task: Differential conditioning task, reinforcement rate: 50% (Figure 1).
Data acquisition: 3 T scanners, 30 axial slices, TR=2sec, TE=30ms, voxel size 3.63x3.63x8mm, interleaved acquisition.
Data analysis: SPMS employing a flexible factorial design (whole brain analysis). Target contrast: R > NR: CS+>CS-. Monte Carlo simulation with minimum cluster size of 142 voxels to correct for multiple comparisons (p < 0.05 corr).

Results

- Although being clinically comparable, brain activation patterns differed between R and NR groups prior to treatment.
- Non-responding was characterized by enhanced activation in the anterior cingulate cortex (ACC) towards a previously presented safety signal (CS-).
- Findings are in line with behavioral studies evidencing deficient safety learning and overgeneralization of conditioned fear in PD patients3.
- Results indicate that ACC activation and deficient safety learning may not only be relevant for the pathophysiology of PD, but also holds a predictive value for treatment response.

Differential fear conditioning task

Table 1. Sample characteristics

<table>
<thead>
<tr>
<th></th>
<th>Responders (n = 24)</th>
<th>Non-Responders (n = 24)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (t)</td>
<td>33.8 (11.2)</td>
<td>37.8 (9.2)</td>
<td>0.04</td>
</tr>
<tr>
<td>CGI (t)</td>
<td>5.32 (0.7)</td>
<td>5.5 (0.7)</td>
<td>0.15</td>
</tr>
<tr>
<td>Ham-A (t)</td>
<td>24.2 (5.4)</td>
<td>25.0 (5.3)</td>
<td>0.24</td>
</tr>
<tr>
<td>ASI (t)</td>
<td>17.4 (9.9)</td>
<td>17.3 (7.4)</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Figure 2. Differences in functional brain activation during the extinction phase in responders (R; n = 24) and non-responders (NR; n = 24) prior to treatment. Effects of interest comparing contrast estimates from each group show that the Anterior cingulate gyrus (ACC) and the right hippocampus (Figure 3 coordinates x=42, y=-18, z=-10) is driven by enhanced activation towards the CS- in the extinction phase in NR, but not R.

Figure 3. Differences in functional brain activation for the interaction effect of acquisition x extinction in responders (R; n = 24) and non-responders (NR; n = 24) prior to treatment. Estimated beta values show that the focus on the right anterior cingulate cortex (ACC) (R: x=42, y=6, z=10) is driven by enhanced activation towards the CS- in the extinction phase in NR, but not in R: p < 0.05; *p < 0.01; **p < 0.001.

Table 2. Brain activation during the fear conditioning task for responders (R) and non-responders (NR).

- Although being clinically comparable, brain activation patterns differed between R and NR groups prior to treatment.
- Non-responding was characterized by enhanced activation in the anterior cingulate cortex (ACC) towards a previously presented safety signal (CS-).
- Findings are in line with behavioral studies evidencing deficient safety learning and overgeneralization of conditioned fear in PD patients3.
- Results indicate that ACC activation and deficient safety learning may not only be relevant for the pathophysiology of PD, but also holds a predictive value for treatment response.

Discussion

- Although being clinically comparable, brain activation patterns differed between R and NR groups prior to treatment.
- Non-responding was characterized by enhanced activation in the anterior cingulate cortex (ACC) towards a previously presented safety signal (CS-).
- Findings are in line with behavioral studies evidencing deficient safety learning and overgeneralization of conditioned fear in PD patients3.
- Results indicate that ACC activation and deficient safety learning may not only be relevant for the pathophysiology of PD, but also holds a predictive value for treatment response.

Study limitations

- Cross-sectional design: future studies should explore this potential vulnerability factor in prospective studies or in high-risk populations.
- Impact of comorbid diagnoses was not evaluated.
- Detected brain activation does not relate to treatment resistance, but to less efficient response (significant improvement also in NR group).
- Results are based on group analyses and will not be applicable for individual response prediction.

Conclusion

If replicated, findings could contribute to a better understanding of how neurofunctional predispositions interact with behavioral treatments and enlarge our knowledge about the pathways by which successful treatments are conveyed.

Recommended Literature

Linke S et al. JAMA Neurol 2013;70:1590-2646.
Kolleck M et al. JAMA Neurol 2013;70:1590;1596.
Glover AT. J Clin Psychol. 2011;70(9):945-920.