Affective flattening in schizophrenia patients: differential association with amygdala response to threat-related facial expression under automatic and controlled processing conditions. An fMRI study

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Introduction: Aberrant amygdala responsivity to emotional faces has been frequently reported in schizophrenia patients (1). Whereas early studies have consistently demonstrated amygdala hypoactivation (2,3), more recent research has found contrary results: Amygdala hyperactivation in patients was shown in paradigms with minimal cognitive load and in paradigms dedicated to automatic affect processing (4,5). Furthermore, hyperactivation was related to symptoms of affective flattening, i.e. lack of emotional reactivity (6). In this study, we investigated amygdala responsivity to threat-related facial expression in schizophrenia patients as a function of processing level, automatic versus controlled, and patients' flat affect, applying a passive viewing paradigm with masked fearful faces for automatic affect processing (7) and unmasked fearful faces for controlled affect processing.

Methods: Functional magnetic resonance imaging was applied to measure amygdala activation in 36 schizophrenia patients and 42 healthy controls aged between 18 and 55 years. Control subjects were checked to be free of any live-time history of psychiatric disorders. Patients' diagnoses were established with the Structured Clinical Interview for DSM-IV (SCID)(8). In addition, patients were tested with a structured protocol of the Scale for the Assessment of Negative Symptoms (SANS) (9). Based on the SANS rating of flat affect patients were assigned to subgroups with and without affective flattening. fMRI stimuli consisted of a sequence with masked emotional facial expression, followed by a sequence with unmasked expressions. Facial expressions displayed were fear, disgust, happiness, and neutral, selected from the KDEF catalogue (10). Subjects viewed 33 s blocks of a facial expression category, projected onto a screen at the rear opening of the scanner. For masked expressions, emotional faces were presented for 33 ms, followed by a 500 ms mask depicting a neutral expression of the same face. In the unmasked expression sequence, the facial emotion was viewed for 533 ms. Each emotion block was followed by a no-face block (skin colored semi oval) and presented twice. Total presentation time was 17 1/2 min. fMRI data were acquired at 3 T (Philips Gyroscan 3.0T) with single shot EPI of the whole brain with 36 axial slices of 3.5 mm, square pixels with 3.6 mm edge length, TR/TE/FA 2.5 s/35 ms/90 deg. Data were evaluated using SPM5, selecting the amygdala as region of interest (11) modeling the emotional conditions as variables. 2nd level analysis focused on the fear versus neutral contrast, with separate analysis of masked and unmasked expression. Relations between amygdala response to masked and unmasked fearful expressions and patient's affective negative symptoms using the SANS score were investigated.

Results: Schizophrenia patients exhibited increased amygdala activation in response to unmasked fearful faces. With respect to masked fearful faces, no between-group differences emerged for the sample as a whole, but a subsample of patients with flat affect showed increased amygdala activation. Amygdala response to masked fearful faces was positively correlated to the degree of flat affect. Conversely, amygdala response to unmasked fearful faces was negatively correlated to the severity of affective flattening. In schizophrenia patients, amygdala responses to masked and unmasked fearful faces showed a strong negative correlation. In controls, this correlation was not significant.

Conclusions: Our findings suggest that amygdala hyperresponsivity to unmasked fearful faces might be a functional marker of schizophrenia. Amygdala hyperresponsivity to masked fearful faces might be a specific characteristic of patients with affective flattening. We assume that flat affect might be a response mechanism to emotional overload by threatening stimuli.

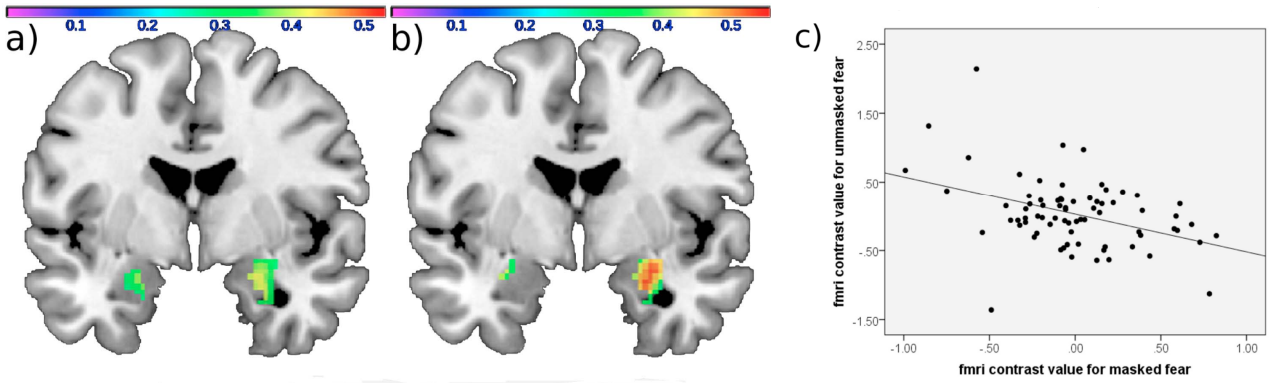

Fig 1: Affective flattening is negatively associated with bilateral amygdala responsiveness to unmasked fearful faces (a) and positively associated with right amygdala responsiveness to masked fearful faces (b) (Coronal View, y = -2, color bar correlation coefficient r). c) In schizophrenia patients, right amygdala responsiveness to masked fearful faces is negatively associated with right amygdala responsiveness to unmasked fearful faces (Scatter plot: negative association between mean cluster activation values, r=-0.55, p=0.001).

References: (1) Anticevic A et al., Schizophr Bull 2012; 38:608-621. (2) Schneider F et al., Schizophr Res 1998; 34:133-142. (3) Gur RE et al., Am J Psychiatry 2002; 159:1992-1999. (4) Blasi G et al., Psychiatry Res 2009; 173:31-38. (5) Holt DJ et al., Schizophr Res 2006; 82:153-162. (6) Gur RE et al., Arch Gen Psychiatry 2007; 64:1356-1366. (7) Dannlowski U et al., J Psychiatry Neurosci 2007; 32:423-429. (8) Wittchen HU et al., Strukturiertes Klinisches Interview für DSM-IV, Hogrefe, Göttingen 2007. (9) Andreasen NC, Br J Psychiatry Suppl 1989; 155:49-58. (10) Lundquist D et al., The Karolinska Directed Emotional Faces (KDEF), Karolinska Institute, Department of Clinical Neuroscience, Stockholm 1998. (11) Tzourio-Mazoyer N et al., NeuroImage 2002; 15:273-289.