**American Journal of Psychology and Cognitive Science**
Vol. 1, No. 2, 2015, pp. 48-60
http://www.aiscience.org/journal/ajpcs

# Subjective Emotional Over-arousal to Neutral Social Scenes in Paranoid Schizophrenia Psychosis Is Significantly Reduced by Effective Antipsychotic Pharmacotherapy

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## Abstract

We have recently found that patients with paranoid schizophrenia experience abnormally *elevated* subjective emotional arousal (SEA) in response to low-arousing/neutral but not to high-arousing/aversive social scenes. The aim of the present study was to test an explanation of this finding by exploring the relative contributions of psychosis and antipsychotic pharmacotherapy. We compared the SEA to the same two types of stimuli in 15 actively psychotic and 15 therapeutically improved post-psychotic inpatients with paranoid schizophrenia contrasted to 30 healthy controls. The results revealed that the SEA to the *neutral* stimuli was significantly higher in the psychotic than in the post-psychotic subgroup, being abnormally high in both of them relative to controls. Conversely, their SEA to the *aversive* stimuli was as high as that of the controls. Additionally, we demonstrated that during psychosis the patients experience low-arousing/neutral scenes as if they are *high-arousing*, thus misattributing *emotional salience* to them. During the post-psychotic phase this deficient differentiation between salient and nonsalient stimuli is partially restored. We discussed how these findings and their explanations could bridge the gap between *objective* neurobiological and *subjective* psychological mechanisms of psychotic-symptom formation and antipsychotic-treatment response, respectively. We argued that an elevated *endogenous* SEA underlies subjective symptoms of psychosis and accordingly is a key target for antipsychotic pharmacotherapy. We further proposed a practical application of our simple SEA-rating-task as a promising neurobehavioral probe for fMRI studies of these mechanisms as well as a potential surrogate endpoint measure of antipsychotic-treatment response, including in clinical trials of novel antipsychotic drugs.

## Keywords

Antipsychotic Pharmacotherapy, Paranoid Schizophrenia Psychosis, Emotional Arousal, Emotional Experience, Emotional Salience Misattribution, Social Cognition

Received: March 31, 2015 / Accepted: April 20, 2015 / Published online: May 27, 2015



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# 1. Introduction

According to the influential circumplex model of emotions [1-5], which has been validated for schizophrenic patients as well [6], the affective states can be characterized by two relatively independent dimensions: valence and arousal. Emotional valence refers to the hedonic tone of an experience ranging from negative/unpleasant to positive/pleasant; while emotional arousal refers to a sense of mobilization ranging from low/inactivated to high/activated. Therefore, all emotions can be understood as combinations of these two basic dimensions [7, 8]. Anxiety and fear, for instance, might be viewed as high-arousal/negative-valence affective states that produce aversive (including paranoid) behaviors [9]. Notably, being an independent dimension, emotional arousal should be discriminated from the intensity of a given (negative or positive) emotional valence [5, 8, 10-12].

Beyond valence and arousal, another important dimension of emotions is their social relevance [13-15]. For example, paranoid anxiety and fear are social emotions that concern non-existing threats from other people and misinterpretation of neutral social environments as hostile, threatening, frightening, and dangerous [16-19]. So, they could be seen as defensive social emotions [16, 18, 20-26]. Accordingly, paranoid delusions [16-18, 27] and hallucinations [28-31] have a distrustful interpersonal orientation [27] or interpersonal sensitivity [19, 23]: the patients are focused on receiving (actually interpreting) messages from outside people (persecutors and/or voices) that provoke avoidant social behaviors [27, 32-36]. Furthermore, abnormalities in affective processing and social cognition are considered to be central features of schizophrenia and psychotic symptoms to represent distortions or errors in comprehending the social world [15, 37]. The fundamental role of defensive social emotions in paranoid schizophrenia has been emphasized by the classical phenomenology, which described the first symptom of incipient psychosis as delusional mood [38] or trema (stage fright) [39], subjectively experienced as anxiety and/or fear associated with (most frequently unconscious) anticipation of some social threats. Delusional mood is typically followed or accompanied by delusional perception, clinically manifested as misattribution of threatening significance to insignificant and innocuous social situations [40-45]. Both delusional mood and delusional perception have been conceptualized to reinforce each other by creating a vicious circle, thus paving the way for delusion formation and hallucinogenesis in paranoid schizophrenia [21]. In the same vein, over-attribution of relevance to otherwise irrelevant social cues has been found to play a prominent role in early stages of schizophrenic psychoses, when patients feel that the world is full of signs that point to a yet unrevealed secret [46]. Likewise, within the framework of the basic-symptom concept of schizophrenia, it has been shown that one of the earliest manifestations of paranoid psychosis is an internally generated hyperalert state of consciousness that mimics the response to external dangers [47]. Anxiety, worry and misattribution of threat to neutral social stimuli have been hypothesized to elicit and further maintain delusion formation and/or hallucinogenesis in paranoid schizophrenia psychoses [16, 21, 48-52]. Consistent with clinical observations and theoretical hypotheses, a meta-analysis of laboratory studies has found that schizophrenic patients experience relatively stronger aversion to neutral stimuli [53]. Moreover, within the categorical model of emotions, which implies a differentiation between a limited number of basic emotions [54, 55], analyses of error patterns have discovered that neutral emotional expressions are misperceived (misinterpreted) as fearful by stable remitted [56] or as angry by acutely paranoid [57] schizophrenic patients. Similar assignment of emotional valence to neutral words was reported in patients with persecutory delusions [58]. Such findings give evidence that patients with paranoid schizophrenia tend to misattribute negative emotional valence to social stimuli that are normally classified as neutral. Analogous threat assignment to neutral social situations has been reproduced using virtual reality experiments in patients with persecutory delusions [59, 60], patients with paranoia [61], individuals at high risk for psychosis [62], individuals who rated higher on trait paranoia [17, 19], and even in some clinically healthy individuals from the general population [50]. The misattribution of threat to neutral avatar behaviors in these experiments was strongly predicted by higher levels of anxiety and worry, thus confirming the important role of defensive emotions for the emergence of paranoid beliefs. Accordingly, the persecutory delusions were conceptualized as affect-laden beliefs regarding other people, which are formed to make sense of and explain increased emotional arousal [63-65].

Our group has previously found that the subjective emotional arousal (SEA) to neutral but not to aversive social scenes was significantly higher in schizophrenic inpatients hospitalized for acute paranoid psychosis than in healthy controls [65]. Recently this finding was essentially supported and somewhat extended by a meta-analysis of 26 studies (including our own) that have investigated the self-reported arousal to a range of affective and neutral stimuli in patients with schizophrenia [12]. The authors concluded that patients and controls report similar arousal in response to affective (pleasant and unpleasant) stimuli, but patients report higher arousal in response to neutral stimuli. Such a conclusion in fact confirms our results [65]. Furthermore, our

neurobiological explanatory hypothesis was supported (though indirectly) by the latest findings that schizophrenic patients not only misattribute emotional importance/salience to neutral stimuli but also activate amygdala and other mesolimbic structures in response to these stimuli to a greater extent than healthy controls [66-68].

The aim of the present study was to better explain the previous empirical findings by dissecting the role of psychosis from that of the antipsychotic treatment. Here we provide a new analysis of our data in order to test the hypothesis that during active psychosis an abnormally elevated baseline level of SEA is misattributed to emotionally ambiguous neutral stimuli but it is subsequently attenuated by effective antipsychotic treatment [65]. We subdivided the schizophrenic group into actively psychotic and therapeutically improved post-psychotic subgroups and compared their SEA in response to the same neutral and aversive social scenes to that of the healthy controls. Based on our theoretical predictions, we anticipated that the SEA to the neutral social scenes would be highest in the psychotic subgroup, relatively lower in the post-psychotic one, and lowest in the control group. In opposition, we expected that the SEA to the aversive social scenes in both schizophrenic subgroups would be as high as that in the control group.

# 2. Materials and Methods

## 2.1. Subjects

This article is based on the previously published study from 30 male schizophrenic inpatients hospitalized for acute paranoid psychosis and 30 matched healthy controls [65]. For our current purposes we subdivided the patients into two subgroups of psychotic (n=15) and post-psychotic (n=15) patients and analyzed their data separately. All three groups – healthy subjects, psychotic and post-psychotic patients – were well matched (see Table 1). There were no significant differences between them on demographic characteristics as age, education and parental education. There was also a good match between the two patient subgroups in terms of their clinical profile. They did not differ in duration of illness, medication and PANSS score for negative symptoms. The differences between the two patient subgroups were based on the study design and were only in terms of PANSS score for positive symptoms and episode duration.

**Table 1.** Demographic and clinical characteristics of participants.

| Variables | Psychotic Patients | Post-Psychotic Patients | Healthy Controls | | |
|---|---|---|---|---|---|
| N Gender | 15 males | 15 males | 30 males | | |
| | Mean±SD | Mean±SD | Mean±SD | F/t | p |
| Age (years) | 37.4±13.42 | 38.67±12.11 | 38.03±12.47 | F(2,57)=.04 | 96 |
| Education (years) | 13.13±2.53 | 14.07±3.83 | 13.60±3.20 | F(2,57)=.31 | 73 |
| Parental Education (years) | 13.30±3.56 | 12.17±3.39 | 13.37±4.18 | F(2,57)=.53 | 59 |
| Clinical profile | | | | | |
| Illness duration (years) | 15.40±10.69 | 13.07±9.68 | N/A | t(28)=-.63 | 54 |
| Medication (mg/day) | 25.67±4.58 | 26.33±3.99 | N/A | t(28)=43 | 67 |
| PANSS: Negative | 20.60±7.77 | 18.00±7.16 | N/A | t(28)=-.95 | 35 |
| PANSS: Positive | 24.13±3.90 | 11.67±2.85 | N/A | t(28)=-9.96 | 001 *** |
| Episode duration (days) | 14.13±7.18 | 35.27±6.56 | N/A | t(28)=8.40 | 001 *** |

Note: SD = standard deviation; N/A = Not applicable; PANSS = Positive and Negative Syndrome Scale; PANSS: Negative = subscale for negative symptoms; PANSS: Positive = subscale for positive symptoms, *** = statistical significance at level p=.001.

Inclusion and exclusion criteria for patients and controls were the same as in the previous study. All patients were hospitalized for an acute psychotic state with well-expressed positive symptoms and all they were on Aripiprazole as monotherapy. The 15 patients included in the psychotic subgroup were investigated as soon as possible after their hospitalization (before being improved by the antipsychotic treatment). On the subscale for *positive* symptoms of the Positive and Negative Syndrome Scale (PANSS) they scored 17 or more with at least one item rated 4 or more. The 15 patients from the post-psychotic subgroup were hospitalized for an acute psychosis as well, but were followed-up until a certain degree of therapeutic remission was achieved before taking part in the study. They were with decreased severity of residual positive symptoms being not yet remitted. On the *positive* subscale of PANSS the post-psychotic patients scored below 17 with no items rated 4 or more.

Informed consent was obtained from all individual participants included in the study. All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

## 2.2. Apparatus, Stimuli and Design Procedure

The task (including the apparatus, stimuli and design procedure) is described in detail in the previous article [65]. Here we provide a brief summary.

### 2.2.1. Apparatus

The experiment was carried out in a quiet laboratory examination room on a laptop with a 14'' diameter screen. The task was administered on a Presentation Software (www.neurobs.com). Stimuli and a rating scale were alternatively projected onto the display.

### 2.2.2. Stimuli

Stimuli were color photographs depicting social scenes - with at least one person presented. They were selected from the International Affective Picture System - IAPS [69] and the Munich Affective Picture System - MAPS [70], so that we can have photos, depicting complex scenes with social content for various dimensions of valence and arousal. For our study we have chosen 10 stimuli with low-arousing/emotionally neutral and 10 with high-arousing/affect-laden aversive content. The *neutral* scenes presented persons attending public events or engaged in work, hobbies or everyday tasks. The *aversive* scenes presented people in situations of abuse, poverty, physical threat, loss, grief, injuries and disaster. Stimuli were selected based on their ratings in the normative MAPS study [70]. The ratings have been based on the Self-Assessment Manikin - SAM [71] on 9-point rating scales for valence and arousal. The neutral and the aversive scenes were matched on size, color brightness, picture complexity, number of depicted persons and format. In addition to the 20 social complex scenes, there were 20 non-social and non-arousing baseline pictures, introduced to neutralize the impression of the scenes by masking their psychological effects.

### 2.2.3. Design and Procedure

Each subject was tested individually. Written and oral instructions were provided together with practice trials prior the actual experiment with individual feedback to assure comprehension both in controls and in patients. Before the experimental task there was a preliminary task to practice rating on the rating scale, which was a moving bar, appropriate and easily applicable in fMRI studies. In the experimental task participants were asked to rate their own subjective emotional arousal (SEA) after seeing a social scene presented on the screen. While a scene was shown subjects had to view it passively and be prepared to rate the evoked level of SEA. The task consisted of 20 trials, randomized across two conditions - aversive and neutral. For further details see [65].

### 2.3. Data Analysis

The study was cross-sectional and we did both within- and between-subjects comparisons. To examine whether the SEA differed across affective categories, depending on group, a 2 x 2 repeated measures ANOVA was used with affective category (low-arousing/neutral vs. high-arousing/aversive) as a within-subjects factor and group (psychotic vs. post-psychotic schizophrenia patients vs. healthy controls) as a between-subjects factor. Planned independent samples t-tests were also performed. All analyses were done with the SPSS software (version 14.0, SPSS Inc., 2000).

## 3. Results

One-way ANOVA revealed a significant group difference in the subjective emotional arousal (SEA) for the neutral social scenes $F(2, 57)=32.48$, $p=.001$, but a lack of group difference for the aversive social scenes $F(2, 57)=1.48$, $p=.24$. To understand between which groups exactly there was a difference in the SEA for the neutral stimuli, independent samples t-tests were made. All three groups differed significantly from one another. Psychotic patients (5.52±1.41) had significantly higher SEA than both the post-psychotic patients (4.02±1.48): $t(28)=-2.85$, $p=.01$ and the healthy controls (2.53±0.88): $t(19.60)=-7.54$, $p=.001$. Post-psychotic patients also had higher SEA than the controls: $t(19.02)=-3.57$, $p=.001$. When we examined the role of the affective category, the paired samples t-tests revealed that in the control group, the SEA for the neutral and for the aversive stimuli was significantly different: $t(29)=-11.75$, $p=.001$. For the post-psychotic patients the difference was only marginally significant: $t(14)=-2.03$, $p=.06$. For the psychotic patients there was a lack of significant difference: $t(14)=-.22$, $p=.83$. (Figure 1)

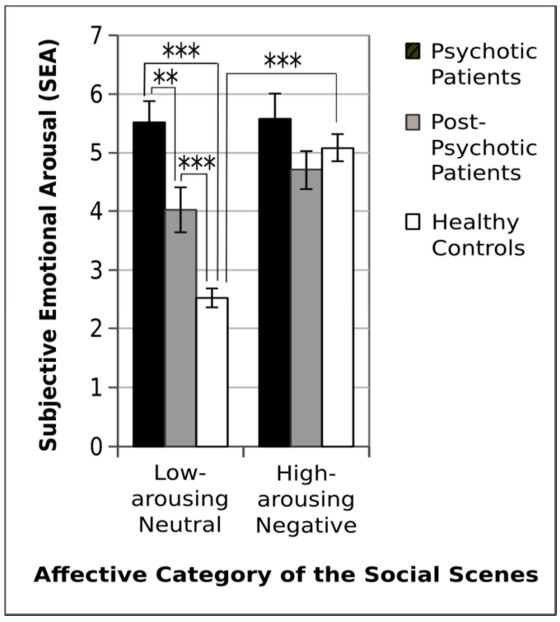


**Figure 1.** Comparison among the subjective emotional arousal (SEA) levels evoked by the 2 affective categories of social scenes in the 3 investigated groups.

** = statistical significance at level p=.01; *** = statistical significance at level p=.001

## 4. Discussion

The present study is the first to explore the role of psychosis and antipsychotic treatment, respectively, for the previously discovered [65] abnormally *high* level of SEA in response to low-arousing/neutral but not to high-arousing/aversive social scenes in patients with paranoid schizophrenia. The empirical fact itself has been subsequently confirmed [12]. There have been data about its supposed neurobiological mechanisms [46, 72-76] that were additionally supported in the last years [66-68]. Now we reveal that the SEA to the *neutral* scenes is significantly *higher* in the actively *psychotic* than in the therapeutically improved *post-psychotic* inpatients, being significantly *higher* in both schizophrenic subgroups relative to healthy controls. This new finding gives evidence that the abnormally elevated level of SEA to the *neutral* social scenes [65] is *highest* during the active phase of psychosis but afterwards (during the early post-psychotic phase) it is significantly *reduced* presumably by the effective antipsychotic pharmacotherapy. On the other hand, the present study reveals that the level of SEA to the *aversive* social scenes in the two schizophrenic subgroups was not different from that of the controls, so it neither depends on the psychotic state nor on the antipsychotic-treatment response. Taken together, these findings attest that the abnormal *elevation* of SEA during the psychotic phase and its *reduction* during the post-psychotic phase of paranoid schizophrenia concern only the low-arousing/neutral but not the high-arousing/aversive social scenes. Hence, the previously revealed abnormal reactivity (oversensitivity) to *neutral* stimuli in schizophrenic patients [12, 65] was validated once again but with the specification that it is associated mainly with the *psychotic* state, whereas the effective *antipsychotic* pharmacotherapy acts in the opposite direction and significantly reduces it.

The findings are consistent with our preliminary hypothesis that the *neurobiological* mechanisms underpinning the *subjective* symptoms of psychosis directly produce an elevated level of baseline SEA (anxious over-arousal or delusional mood), thereby inducing intolerance of ambiguity, which results in *oversensitivity* to neutral (non-salient) social scenes and aberrant assignment of emotional salience to them [65]. In the context of emotional tasks, the *neutral* social stimuli are indeed *ambiguous*, since they do not possess their own unambiguous emotional valence (positive or negative) nor they evoke considerable SEA in healthy controls. Psychotic patients might be particularly sensitive to such stimuli as they are intolerant of ambiguity and inclined to make hasty decisions (e.g. jumping to conclusions or threat assignment) in *ambiguous* social situations [48, 52, 63, 77-82]. Intolerance of ambiguity has been usually associated with anxiety and worry [83-86] and previous studies have found that *anxious* patients tend to appraise *ambiguous* social stimuli as more dangerous and to classify them as threatening [87], i.e. as high-arousing/aversive. It was documented that anxious patients and healthy controls similarly appraise unambiguous threats, but the anxious patients appraise *ambiguous* threats as more dangerous than do healthy controls, thus demonstrating a compromised capacity to separate safety from threat and a failure to inhibit fear responses in safe contexts [87]. A recent cognitive model of delusion formation in paranoid schizophrenia (paranoia) has assumed *psychotic* social anxiety to be a key emotion that leads to a search for meaning and explanation, thus contributing to creation of threat beliefs [17, 52, 59, 63, 88]. Accordingly, persecutory delusions have been viewed as compensatory attempts to explain the unjustified social anxiety and *increased* anxious arousal [63, 64, 89-90]. Such concepts are based on the idea that similar mechanisms might elicit paranoid and anxiety states [51, 52, 63, 82, 88, 91-94]. At the same time, both these states could be seen as resulting from abnormal *regression* (though to a different degree) toward earlier *immature* phases of emotional development [21, 22]. Although *neutral* social stimuli normally indicate safety, their social significance might be distorted in *immature* children, who exhibit *greater* amygdala activation in response to *neutral* than to fearful faces, indicating that, until discrimination and appraisal processes mature, *neutral* social stimuli are deemed more *ambiguous* [87, 95, 96]. Notably, similar data for *overactivation* of the amygdala [66-68, 72] and other limbic structures [46, 73, 75, 76] in response to *neutral* faces have been reported in psychotic schizophrenic patients and subjects at high risk for psychosis.

Our present study demonstrates the fact that during active psychosis the level of SEA to *neutral* social scenes is comparable to that of the *aversive* ones. This fact suggests that *psychotic* patients perceive *ambiguous* (low-arousing/neutral) social stimuli as if they were high-arousing/aversive and thus *unconsciously* misattribute emotional salience to them. As psychotic patients are *basically* over-aroused [97-99], it is conceivable that they fail to inhibit their abnormally elevated baseline SEA in safe (neutral) contexts, while keeping their *normally* high SEA in aversive contexts. Other studies have also demonstrated abnormalities in the ability of *psychotic* patients to discriminate between motivationally *salient* and *neutral* stimuli [66, 68, 73, 100-103]. Theoretically, such findings are explainable by a malfunction of the fundamental human capacity to differentiate safe from dangerous social stimuli, which is learned throughout early development [87, 95, 96]. Analogous failure to distinguish between threat and safety might explain why schizophrenic patients experience

stronger *aversion* to neutral stimuli [53] and tend to misattribute *negative* emotional valence to them [56-58].

At a more neurobiological level, this inability of schizophrenic patients to discriminate between neutral and aversive social stimuli could be explained by the influential "aberrant salience hypothesis" [104-108], which postulates that during psychosis an exaggerated release of dopamine in the mesolimbic system occurs out of context and independent of the situation. Thus dopamine, which under normal conditions is a mediator of contextually relevant salience, in psychotic states becomes a creator of aberrant salience to otherwise irrelevant *neutral* stimuli. The process is often associated clinically with a sense of *anxiety* [107], i.e. a high-arousal/aversive emotional state. The aberrant salience hypothesis has been admitted and/or validated by many researchers in the field [46, 58, 81, 109-120]. A related hypothesis has also postulated that during psychosis an imbalance in dopamine systems underlies increased anxiety (over-arousal) and the assignment of *emotional* salience to insignificant *emotionally* neutral stimuli [72]. Notably, the causal role of dopamine increase for the misattribution of aberrant salience to task-irrelevant *neutral* stimuli has been recently revealed in previously never-medicated patients with Parkinson's disease after starting their treatment with dopamine *agonists* [121] and analogous misattribution of relevance to task-irrelevant *neutral* stimuli has been demonstrated experimentally after administration of amphetamine in healthy volunteers [122]. Hence, we might assume that the elevated level of *endogenous* SEA in psychotic patients, which leads to misattribution of salience (relevance, importance) to otherwise nonsalient *neutral* stimuli, might be explained by the same exaggerated and chaotic firing of mesolimbic dopaminergic neurons, out of context and independent of the situation, which has been conceptualized by the aberrant salience hypothesis [104]. Such an explanation is in line with our finding that the antipsychotic pharmacotherapy significantly reduces the abnormally elevated SEA to neutral social scenes.

Moreover, our hypothesis for a *neurobiologically* generated (endogenous) subjective emotional *over-arousal* (aberrantly assigned to *neutral* social scenes) could be supported by the recent functional-neuroimaging data for *overactivation* of limbic structures, like the amygdala [46, 66-68, 72, 76, 103], the hippocampus [75, 105], and the parahippocampal gyrus [73] to *neutral* social stimuli in prodromal and/or *psychotic* schizophrenic patients. Other studies have provided direct evidence that inappropriate activation of the amygdala, the midbrain, and the ventral striatum in response to *neutral* stimuli is associated with the severity of delusional symptoms in patients with schizophrenia [76]. Additional neuroimaging evidence has been accumulated about *overactivation* of cortical midbrain network during emotional and/or social appraisals in schizophrenia [11, 34, 37, 66, 101, 123], especially during psychosis [33]. Previous research suggests that psychotic-symptom formation (reality distortion dimension) of paranoid schizophrenia is linked with an endogenous *overactivation* of limbic structures that are part of the "fear systems" [74] within the emotional brain [124], which are normally activated in case of *external* danger [124-127] and some of them (e.g. the amygdala) are involved in the detection and attribution of salience [128]. A number of studies on emotional processing in schizophrenia have found evidence for a behavioral bias or an *elevated* neural response to affectively *neutral*, nonsalient stimuli during emotional processing [56, 58, 73, 74, 100, 101, 103, 113, 129], which in some studies has been linked to psychotic symptoms [73, 130, 131] or specifically to paranoid delusions [58, 113, 129, 132]. This abnormal brain response to neutral stimuli has been proposed to reflect a tendency to attend preferentially, or misattribute motivational salience, to nonsalient information during psychotic states [104, 105] and has been linked to abnormalities in emotional appraisal [37, 103, 131, 133]. Based on our present data, we may theorize that during active psychosis an overactivation of the limbic system elicits a state of abnormally elevated baseline SEA, which is "projected" to ambiguous, nonsalient (emotionally neutral) social stimuli, thus leading to aberrant assignment of emotional salience to them. By unifying the different levels of explanation, we might generalize that *psychotic* patients are emotionally over-aroused and thus oversensitive to emotionally neutral (ambiguous) social stimuli due to underlying mesolimbic hyperdopaminergia [46, 104-120] and/or overactivation of the "fear systems" within the limbic brain [74, 130].

Just in the opposite direction is the explanation of our finding that during the *post-psychotic* phase of paranoid schizophrenia, the level of SEA to neutral but not to aversive social scenes is significantly *lower* than during active psychosis. This finding might shed new light on the mechanisms of the antipsychotic-treatment response and could be explained by the propensity of the antipsychotic pharmacotherapy to restore the deficient selective inhibition of the context-inappropriate high SEA to neutral stimuli, while preserving the context-appropriate high SEA to aversive stimuli. It is logical to assume that the post-psychotic patients partially succeed to differentiate safety from threat and to inhibit their abnormally elevated SEA to neutral social scenes, thus approximating the healthy controls. Our explanation of this tendency toward normalization is that (by dampening the abnormally high level of *baseline* SEA) the antipsychotic pharmacotherapy *reduces* the oversensitivity to ambiguous (emotionally neutral) social

stimuli and thus dampens the misattribution of emotional salience to them. In fact, both psychotic and post-psychotic patients experience significantly higher SEA to neutral but not to aversive social scenes relative to healthy controls. So, both schizophrenic subgroups fail to selectively inhibit their inappropriately elevated endogenous SEA in neutral social contexts, but this deficient selective inhibition is partly restored (though not normalized) in the post-psychotic subgroup. We may admit that the antipsychotic treatment selectively dampens only the *inappropriately* high SEA to *neutral* social stimuli, while leaving almost unaffected the *appropriately* high SEA to *aversive* stimuli. It appears that the antipsychotic pharmacotherapy *selectively* inhibits the *abnormally* high level of *endogenous* SEA and thus prevents its external projection to emotionally ambiguous neutral social scenes, but keeps relatively intact the *normally* high level of *exogenous* SEA evoked by unambiguously high-arousing aversive scenes. Therefore, according to our interpretation, the antipsychotic mechanisms are selectively focused on the *internally* but not on the *externally* generated high level of SEA. To the best of our knowledge, such a mechanism of the antipsychotic treatment has not been discussed until now. In principle, it could be incorporated in the mechanism postulated by the above mentioned aberrant salience hypothesis [104-108], which admits that antipsychotic drugs are efficacious because (by suppressing the underlying mesolimbic hyperdopaminergia) they dampen the aberrant salience misattributed to otherwise *neutral* stimuli [104-108, 115, 117, 119]. Our present data might explain how the reduction of mesolimbic hyperdopaminergia dampens the aberrant assignment of *emotional* salience to neutral (nonsalient) social stimuli. According to our interpretation, the effective antipsychotic pharmacotherapy not only suppresses the mesolimbic hyperdopaminergia but also dampens the *overactivation* of the fear (defense) systems in neutral (safe) contexts, thereby selectively attenuating the elevated *endogenous* SEA and its misattribution ("projection") to low-arousing/neutral social stimuli. A direct confirmation of such a hypothesis would be achieved relatively easy by analogous comparisons between the SEA ratings of psychotic and post-psychotic patients with paranoid schizophrenia during functional-neuroimaging (fMRI) recordings, since our task was explicitly designed just for this type of research [134]. We expect a significant *overactivation* of limbic structures (particularly the amygdala) in response to neutral but not to aversive social scenes during active psychosis and its relative reduction during the post-psychotic phase of the illness. It is worthy to note that ratings of SEA have already been successfully used to discriminate between fMRI-data of different subgroups of patients and healthy controls [135, 136].

From a more practical point of view, we could argue that the level of SEA to neutral social scenes might serve as a proxy measure of the *neurobiological* mechanisms of both psychotic-symptom formation and antipsychotic-treatment response in patients with paranoid schizophrenia. So, its abnormal elevation during active psychosis might be used as a subclinical state-marker for psychosis as well as a surrogate measure of the level of yet inaccessible mesolimbic hyperdopaminergia supposedly underlying the psychotic state [110, 115, 117, 119]. Correspondingly, we could predict that its degree of relative attenuation during the post-psychotic phase might be used as a surrogate endpoint measure of the antipsychotic-treatment response. Importantly, if our assumptions prove to be true, then our simple, not expensive and easy-to-perform task with SEA ratings could be applied as a promising neurobehavioral probe for fMRI-studies of the pro-psychotic and anti-psychotic brain mechanisms, respectively [134]. It could be successfully applied in the everyday practice for *subclinical* treatment monitoring, including in clinical trials of novel antipsychotic drugs [137]. Future research with a follow-up (prospective) design would be necessary to verify the feasibility of these perspectives.

The present study is only an initial step to a more profound explanation of the mechanisms that underlie psychotic-symptom formation in paranoid schizophrenia and their suppression by effective antipsychotic treatment, particularly within the framework of the new field of SEA. Together with the above discussed advantages, the present study has some limitations. One of them is the fact that we have investigated only males, aiming to select more homogenous groups and to prevent the confounding role of gender. Therefore, future studies that comprise females would be necessary to enhance the generalization of our results. Concerning the generalization of the theoretical interpretations, we should admit that they are not yet conclusive due to the relatively small size of the investigated groups. However, we claim that the conceptual basis of our explanations is solid enough to allow plausible assumptions that would serve at least for further hypothesis-testing efforts. Another issue that should be considered is that we have measured only the level of SEA, because we have been particularly concerned with the *subjective* experience of patients with paranoid schizophrenia. Having in mind that tonic electrodermal hyper-arousal is part of a transient intermediate state that may lead to a psychotic episode in vulnerable individuals [97], in future studies it would be interesting to include some objective measures of autonomic arousal [97-99, 138-140], such as skin conductance response, heart rate, pupilometry, and electroencephalography, in order to compare them with the level of SEA. As a next step, a direct functional neuroimaging recording during the execution of the task

would help to reveal the brain mechanisms that underlie the SEA to affective and non-affective stimuli in patients and controls. Furthermore, it would be important to replicate the findings with a longitudinal study.

There are many directions for more research on the topic [141]. Further analyses could take into account the reaction-time measures and the content of the different neutral social scenes. It would be also recommendable to compare the SEA to the same stimuli in different psychotic syndromes, such as hallucinatory vs. delusional, as well as acute vs. chronic psychoses. It would be interesting to use analogous neutral social stimuli from other modalities, e.g. by using audio stimuli with social significance from the International Affective Digitized Sound System [142]. An acoustic task may be even more sensitive in patients with paranoid schizophrenia, particularly during the phase of florid psychosis, because the difficulty to detect and recognize ambiguous sounds would stimulate the patients to project their dominant emotional experiences, especially paranoid fears, since the acoustic modality is specifically associated with unseen or hidden threats and dangers [48, 79]. Another direction is to study *non-psychotic* schizophrenic patients, e.g. during stable therapeutic remission or long-term deficit states. Longitudinal follow-up studies of the level of SEA to low-arousing/neutral and high-arousing/affective social scenes in never medicated psychotic patients (before and after treatment) could also provide valuable results. Last but not least is the option to include high-arousing/positive, low-arousing/positive and low-arousing/negative social scenes in future research of the level of SEA in other fields of psychiatry and clinical neuroscience.

## 5. Conclusion

The present study is the first to provide evidence that the previously revealed abnormally high level of SEA to low-arousing/*neutral* social scenes in patients with paranoid schizophrenia is psychotic-state related and accordingly it is significantly *reduced* by effective antipsychotic treatment. At the same time, the SEA evoked by high-arousing/aversive social scenes is neither depending on the psychotic state nor on the antipsychotic pharmacotherapy. To explain these crucial findings we propose a hypothesis that subcortical (limbic) mechanisms of psychotic-symptom formation directly produce an abnormally elevated baseline SEA, which then is unconsciously projected (misattributed) to low-arousing/neutral social stimuli, due to their emotional ambiguity. Afterward, the effective antipsychotic pharmacotherapy acts in the opposite direction. By suppressing the neurobiological mechanisms of psychosis it tends to restore the selective inhibition of the inappropriately high SEA in safe contexts, while preserving the normally high SEA in aversive contexts. So, the effective antipsychotic pharmacotherapy selectively dampens the *internally* generated SEA, thus reducing its misattribution to low-arousing/neutral stimuli, while keeping the *externally* generated SEA, evoked by high-arousing/aversive stimuli. The revealed mechanisms of SEA would represent the missing link between the objective (brain) and subjective (mind) mechanisms of both psychotic-symptom formation and subsequent antipsychotic-treatment response. From a theoretical point of view, this would contribute to bridge the explanatory gap between the basic objective disease process in the brain and the resulting subjective experiences not only during the transition from acute psychosis to post-psychotic remission but also during the mirror transition from pre-psychotic high-risk and prodromal states to full-blown psychosis [143-147]. So, our findings could have important theoretical and practical implications in the very promising field of early detection and preventive treatment of such states.

## Acknowledgements

We gratefully acknowledge the financial support from the Bavarian Research Foundation (Bayerische Forschungsstiftung) within the Neuro-Cognitive Psychology (NCP) Program and DAAD. The German Research Foundation (DFG, IRTG 1328) and Medical University, Sofia also provided partial funding for the project. We appreciate the contribution of Anna Beraldi for the preliminary selection and evaluation of the stimuli. We also wish to thank Diana Shkodrova, MD, PhD for the helpful discussions and for her valuable inputs and useful comments on the study and the manuscript.

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