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MISATTRIBUTION OF EMOTIONAL OVER-AROUSAL TO NEUTRAL FACES IN ACUTE PARANOID SCHIZOPHRENIA PSYCHOSIS

Evelina Haralanova[1,2], Emil Milushev[3,4], Ángel José Martín Gargiulo[5], Mercedes María Lucrecia Gargiulo[5], Augusto Pascual Ítalo Gargiulo[5], Marcos Constantino Josué Gargiulo[5], Manuel Alejandro Guevara[5], Adriana Inés Landa De Gargiulo[5], Norman Darío López[6], José Vicente Lafuente[7], Pascual Ángel Gargiulo[5,8] & Svetlozar Haralanov[1,2]

1. Medical University of Sofia, Sofia, Bulgaria, Department of Psychiatry and Medical Psychology.
2. University Hospital for Neurology and Psychiatry "St. Naum", Sofia, Bulgaria, First Psychiatric Clinic.
3. Medical University of Sofia, Sofia, Bulgaria, Department of Neurology.
4. University Hospital for Neurology and Psychiatry "St. Naum", Sofia, Bulgaria, Neurological Rehabilitation Clinic.
5. Laboratory of Neurosciences and Experimental Psychology. Fundación Corporación Tecnológica Latinoamericana (FUCOTEL). Area of Pharmacology, Department of Pathology. Faculty of Medical Sciences. National University of Cuyo. National Council of Scientific and Technological Research (CONICET, Argentina). Mendoza, Argentina.
6. Departamento de Ciencias Sociales. Universidad de La Costa. Barranquilla, Colombia.
7. Laboratorio de Neurociencias Clínicas y Experimentales. Departamento de Neurociencias. Universidad del País Vasco.
8. Cathedra of Psychopathology. Faculty of Humanities and Economical Sciences. Catholic University of Argentina. Mendoza, Argentina.

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Summary

Introduction: *Misattribution of motivational salience to non-salient (neutral) stimuli could be viewed as a hallmark of psychosis in schizophrenia. Studies have recently revealed increased subjective experience of emotional arousal (EA) to neutral social stimuli in paranoid schizophrenia psychosis, suggesting a misattribution of emotional salience to them. We examined this phenomenon directly by quantifying the level of EA subjectively attributed to low-arousal, neutral-valenced faces.*

Subjects and Methods: *A task for EA attribution to neutral (in the context of affective) facial expressions was applied to 44 actively psychotic paranoid schizophrenia inpatients and 44 well-matched healthy controls.*

Results: *Psychotic patients, compared with healthy controls, rated the neutral faces as more aroused (t (86) = 3.15, p =.001) thus misattributing emotional salience to them.*

Discussion: *This finding supports the hypothesis that over-assignment of EA to neutral faces could be viewed as a subclinical affective mechanism of the clinically manifested experience of delusional perception.*

Conclusion: *The study provides the first direct empirical evidence for misattribution of emotional salience in terms of over-attribution of EA to neutral faces during acute paranoid schizophrenia psychosis.*

Keywords: *Schizophrenia, misattribution, neutral, stimuli, delusion, perception, emotional salience.*

* * * * *

INTRODUCTION

Facial expressions are important for social interaction as they convey information about other individuals' emotions and social intentions, as well as about their current mental states. It is well established that patients with schizophrenia have substantial deficits in facial emotion perception and recognition (Corcoran et al. 2015, Gabay et al. 2015, Heimberg et al. 1992, Irani et al. 2012, Kohler et al. 2000, 2003, 2010, Mier & Kirsch 2017, Pinkham et al. 2007, 2011, Savla et al. 2013). It might be associated with impaired affective theory of mind or deficient attribution of emotion (Mier et al. 2010, Savla et al. 2013). It has been suggested that such trait-like social-cognitive *deficits* might predispose to a psychotic state-related social-cognitive *production* or aberrant attribution of emotional state to neutral facial expressions (Haralanov & Haralanova 2009, Shkodrova et al. 2007). These deficits could be clinically manifested by unfounded subjective experience that unknowns stare at them, look at them strangely, smile ironically or frown without apparent reason and seemingly express disapproval, antipathy, disgust, anger or hate. Such abnormally biased facial emotion perception demonstrates that psychotic paranoid schizophrenia patients are prone to assign aberrant emotional salience to non-salient

neutral-valenced facial expressions (Haralanova et al. 2009a, 2009b). Phenomenologically it might be viewed as delusional perception (Jaspers 1913, Fuchs 2005). In the same vein, studies have reported that schizophrenic patients tend to mislabel neutral facial expressions as threatening (Green & Phillips 2004, Phillips 2011) or angry (Habel et al. 2010, Pinkham et al. 2011) during acute psychosis and as fearful or disgusted (Kohler et al. 2003, Habel et al. 2010) during more chronic or post-psychotic states. A similar overattribution bias toward labeling neutral faces as negative-valenced has been reported in individuals at high clinical and/or familial risk for psychosis, i.e. during pre-psychotic states (Eack et al. 2010, van Rijn et al. 2011).

Regarding neural correlates of facial affect misattribution, a large body of functional neuroimaging research has revealed abnormal overactivation of "fear systems" during perception of neutral faces in pre-psychotic and psychotic states (Habel et al. 2010, Hall et al. 2008, Holt et al. 2006, Lakis & Mandrek 2013, Modinos et al. 2015, Potvin et al. 2016, Regenbogen et al. 2015, Seiferth et al. 2008, Surguladze et al. 2006). Thus, clinical, neurocognitive and neuroimaging studies indicate that paranoid schizophrenia psychosis might be associated with a tendency to misattribute undue emotional salience to neutral faces.

Notably, most influential studies of facial emotion perception and recognition in schizophrenia (e.g. Eack et al. 2010, Gur et al. 2002, Habel et al. 2010, Kohler et al. 2003, 2010, Pinkham et al. 2011, van Rijn et al. 2011) have been carried out within the categorical model of basic emotions (Ekman 1992, Izard 1992), which implies that a given facial emotion is recognized and categorized by a corresponding labeling, and subsequently classified dichotomously as correct or incorrect. Hence, the patients' misattribution of emotional salience to neutral faces has been usually considered to be an error pattern of facial emotion recognition (Kohler et al. 2003) without being quantified dimensionally.

However, human emotions have been also characterized by underlying two-dimensional space of valence and arousal, which permits their more precise quantitative assessment. In this model emotional valence (EV) refers to the hedonic tone of an experience, ranging from negative/unpleasant to positive/pleasant, while emotional arousal (EA) refers to the subjective sense of activation, ranging from low/inactivated to high/activated (Kuppens et al. 2013). According to the related circumplex model (Gerber et al. 2008, Russell 1980), which has been validated for schizophrenia patients too (Kring et al. 2003), all human emotions can be understood and measured as combinations of these two orthogonal dimensions. Therefore, the available clinical and laboratory data could be (re) interpreted as an indication that patients with paranoid schizophrenia tend to misattribute negative EV to facial expressions that are normally classified as neutral (Cohen & Minor 2010).

Looking at the other side of the coin (Llerena et al. 2012), the same data might indicate that such patients are prone to misattribute higher EA to actually low-aroused neutral-valenced faces (Haralanova et al. 2009a, 2009b), since the misattributed facial emotions like fear, anger, and disgust are associated not only with negative EV but also with high EA.

In a previous study, according to Conrad ideas regarding a gestaltic dysfunction in the incipient schizophrenia (Conrad 1966), we found that schizophrenic patients failed in the execution of the Gestaltic Bender test (Del Vecchio & Gargiulo 1992). It implies that the shape map construction is affected, and it may be closely related to misperception. It may be the case here, involving human faces perception. If this fact is related to delusional mood ("trema" in Conrad terms), the perception difficulty may add the signification of a possible danger or threat, with a high emotional load. It could be also the case here.

The aim of the present study was to quantify the level of EA subjectively attributed to neutral faces by paranoid schizophrenia patients with acute psychosis compared with well-matched healthy control subjects. Based on our previous pilot studies (Haralanova et al. 2009a, 2009b), we anticipated that patients would misattribute significantly higher level of EA than controls to ambiguous (ambivalent) facial stimuli, thereby projecting their own internally generated emotional over-arousal to them (Haralanova et al. 2008, 2012, Llerena et al. 2012).

SUBJECTS AND METHODS

Subjects

The sample consisted of 44 paranoid schizophrenia patients hospitalized for acute psychosis in the First Psychiatric Clinic of the University Hospital for Neurology and Psychiatry "St. Naum" at Sofia (Bulgaria) and 44 healthy controls. The groups were matched on gender (all males), age and years of parental education. All participants were males due to the gender specialization of the clinic. Age range of the subjects was between 18 and 40. The mean age for healthy controls was M = 27.50 ± SD = 5.59 and for the patients: M = 28.93 ± SD = 5.97, t (86) = 1.16, p=.25. The mean parental education of healthy controls was M =13.49 ± SD = 2.34 and for the patients: M

=12.85 ± SD = 2.43, t (84) =1.25, p =.21. Inclusion criteria for patients were: diagnosis of paranoid schizophrenia (F20.0), according to the ICD-10 criteria, based on the ICD-10 Symptom Checklist (Janca et al. 1993). Exclusion criteria for patients and controls were: history of or current (concomitant) psychiatric or neurological disorders; alcohol or substance abuse; mental retardation (IQ below 85); lack of ability or desire to provide informed consent. The study was approved by the ethical committee of the University Hospital for Neurology and Psychiatry "St. Naum" at Sofia (Bulgaria) and has been carried out in accordance with the latest version of the Declaration of Helsinki. Before inclusion in the study and after the nature of the procedures had been fully explained and all subjects provided written informed consent.

Apparatus

Testing took place in a quiet examination room located within the closed-door acute-psychosis ward. This assured that psychotic patients would not be excluded due to symptom severity. The test was computerized and was performed on a laptop with a 14" LCD screen, resolution of 1024 x 768 pixels, 96 dpi, and a refresh rate of 60 Hz. Presentation Software (www.neurobs.com) was used for test preparation and administration. Subjects were placed at a comfortable distance from the laptop. Stimuli were projected onto the display and responses were given by pressing a button on the keyboard.

Experimental procedures

Each subject was tested individually. Written and oral instructions were provided. The focus of the study was to examine ratings of emotional arousal for emotionally neutral faces. Before the experimental task, the rating scale was shown on its own and explained. Prior to the actual experiment there was an example trial with individual feedback to assure comprehension.

Stimuli

The stimuli were 8 photographs of actors and actresses from various cultures with emotionally neutral and low-aroused facial expressions. They were selected from the Facial Emotions for Brain Activation set of stimuli (Gur et al. 2002). The neutral faces were presented in the context of emotional and high-aroused facial expressions balanced on valence: 8 negative (angry) and 8 positive (happy) faces. Thus, the overall number of photographs was 24, all with the same size and format. Faces were presented on a black background.

Experimental task

The task was to rate on a nine-point scale the level of emotional arousal of persons shown in color photographs. The question was: "What is the level of emotional activation of the person?" Subjects were instructed to choose a number from 1 to 9, where 1 corresponded to lack of emotional activation and 9 – to maximum emotional activation of the person in the photo. The goal was to respond as quickly and spontaneously as possible, by pressing the chosen number on the keyboard. The two ends of the emotional-arousal (activation) rating scale represented two opposite emotional-arousal states: calm (low-aroused) versus excited (high-aroused). A trial begins with a presentation of a stimulus, either neutral or affective. After 1 s the stimulus disappears and is replaced by the emotional-arousal rating scale. It stays on the screen until a response is given. If there is no response in the next 10 s, then there is a blink for 300 ms and the scale reappears for another 20s. Thus, there is enough time for response to assure that all stimuli would be rated. The inter-trial interval is 2 s, during which a black screen appears. The procedure within a single trial is illustrated on Figure 1.

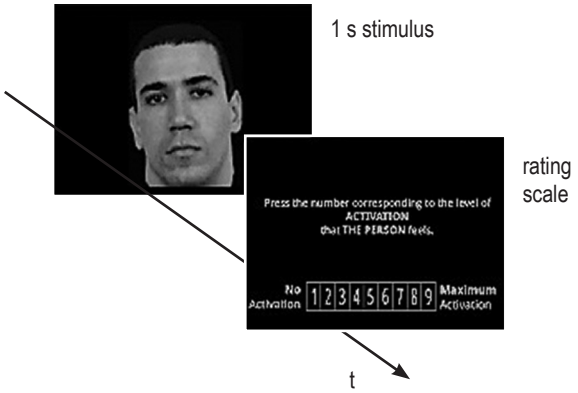

Figure 1. Single trial. Display of a stimulus for 1s, followed by the assessment on the attribution-of-arousal-rating-scale.

Data Analysis

The study was cross-sectional and we performed between-subjects' contrasts. Independent samples t-tests were performed to examine whether the attribution of emotional arousal differed between patients and controls. All analyses were done with the GNU PSPP software (version: psppire 0.7.9, http://www.gnu.org/software/pspp/).

Ethical Approval

All investigated persons (patients and healthy controls) have signed written informed consent before their participation in the study. The study protocol and the informed consent form of the study were approved by the local ethics committee of the University Hospital for Neurology and Psychiatry "St. Naum" in Sofia, Bulgaria (where the patients and healthy controls were investigated).

RESULTS

Independent samples t-tests revealed a significant difference between the schizophrenia and the healthy control group in their ratings for the neutral faces: t (86) = 3.15, p = .001. The neutral faces were rated as more aroused by the schizophrenia patients (M = 3.9 ± SD = 0.21) than by the healthy controls (M = 3.07 ± SD = 0.16). In other words, paranoid schizophrenia patients misattribute emotional arousal (emotional salience) to neutral (non-salient) faces (Figure 2).

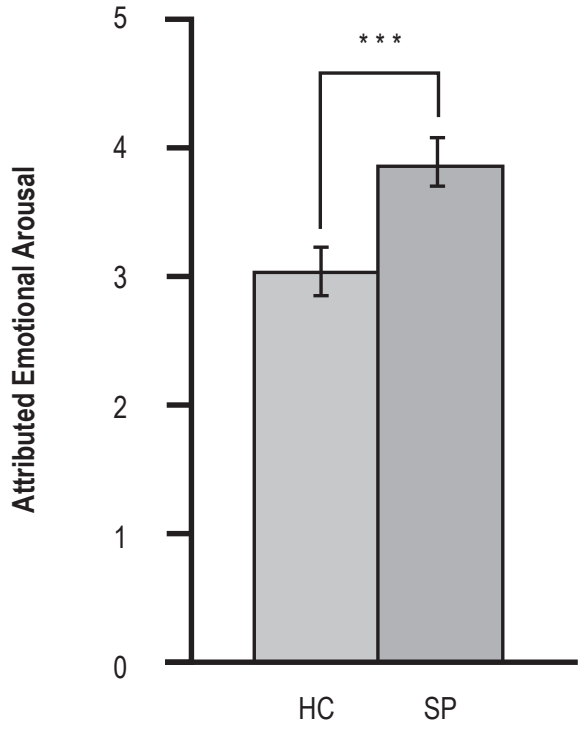

Figure 2. Attributed Emotional Arousal. There is increased attribution of emotional arousal to neutral faces in schizophrenia patients (SP) compared to healthy controls (HC).

**** The difference is significant at p=.001.*

DISCUSSION

The present study is the first specifically designed to examine the level of emotional arousal misattributed to neutral facial expressions by psychotic paranoid schizophrenia patients compared with healthy control subjects. The main finding is that the level of EA ratings to neutral expressions is significantly higher in patients relative to controls. Such a finding is in line with our previous pilot studies (Haralanova et al. 2009a, 2009b) as well as with our preliminary hypothesis that psychotic patients are prone to externalize or misattribute the source of their internally generated subjective emotional over-arousal to neutral (low-aroused) social stimuli (Haralanova et al. 2008, 2012). Thus, a plausible phenomenological explanation of the present finding would be that during acute paranoid psychosis a subjective experience of delusional mood (Heinz 2002, Jaspers 1913, Mishara 2010) and emotional over-arousal (Haralanova et al. 2008, 2012) might be projected to neutral faces due to their emotional ambiguity. Misattributing emotional over-arousal to neutral facial expression could be considered as fundamental to delusional perception (Fuchs 2005, Jaspers 1913, Haralanov et al. 2015).

Clinically, the quantified level of EA misattributed to neutral faces might serve as a proxy measure of the neurobiological mechanisms of psychotic-symptom formation in patients with paranoid schizophrenia. Thus, abnormal over-arousal during active psychosis might be used as a subclinical state-marker for psychosis as well as a subjective but quantifiable surrogate measure for the level of the yet inaccessible mesolimbic hyperdopaminergia (Henn 2011) or glutamatergic corticostriatal projection decrease (hypoglutamaatergia) supposedly underlying the psychotic state.

Starting from our clinical approaches regarding misperception of schizophrenic patients in Bender Gestalt test (Del Vecchio & Gargiulo 1992, Gargiulo 2001), we proposed a translational approach to perception failure in schizophrenia, studying perception in pigeons. Putative brain schizophrenia neurotransmitter disorders were induced in pigeon brain and after it in rat brain.

Experiments in pigeons and rats consisted in the administration of dopaminergic agonists and glutamatergic N-Methyl-D-aspartic acid (NMDA) antagonists within Nucleus Accumbens Septi (NAS) using bilateral stereotaxically implanted cannulae. NAS constitutes the end nucleus of the dopaminergic mesolimbic pathway, and the main target of antipsychotic drugs. It is also a final end for some glutamatergic projections coming from hippocampus, amygdala and prefrontal cortex (Grace 2000,

Llano López et al. 2013). In implanted pigeons trained to discriminate visual stimuli, we observed that dopaminergic NAS stimulation did not led to a failure in shape discrimination. However, NMDA antagonists led to a decrease in discrimination near chance levels when injected within NAS. We concluded that disruption of glutamatergic NMDA transmission within NAS should be considered as the main mechanism of schizophrenic psychosis (Gargiulo et al. 1998, 2005, Acerbo et al. 2002). Furthermore, translational homologous signs of secondary symptoms were also proposed in pigeons (Gargiulo et al. 1998, 2005, Acerbo et al. 2002) and rats (Martínez et al. 2002a, 2002b, Gargiulo et al. 2018, 2020). In the cognitive sphere, working memory disturbances were also induced in this way by us in rats with a concomitant prefrontal cortex hyper activation. We used again here NMDA glutamatergic antagonists within rat NAS (Baiardi et al. 2007). Dopaminergic inhibitory D2 terminals end very near of excitatory NMDA glutamatergic terminals in ventral striatal neurons (Kelley et al. 2003). A balance is present between dopamine and glutamate in the NAS, and an imbalance between dopamine and several glutamatergic projecting pathways may explain the schizophrenic psychosis symptomatology (Gargiulo et al. 1998, 1999, 2001, 2003, 2020, Grace 2000, Gargiulo & Landa 2004, 2014). We considered very relevant the role of translational approaches to psychiatric disorders (Gargiulo et al. 2015).

Fear recognition has been also widely studied in relation with serotoninergic transmission using selective serotonin re-uptake inhibitor (SSRI) treatment (Norbury et al. 2007). The underlying mechanisms may be explained as linked with these neurotransmitter systems and, mainly, with 5-HT3 receptors (Harmer et al. 2006).

The 5-HT3 antagonists have been proposed for certain conditions related to unconditioned fear, such as panic attacks or phobic disorders, without affecting memory. These would be various clinical pictures linked to fears related to ethological variables (Gargiulo et al. 1996). This has been proposed by us as an explanation for the contrasting effects of the results obtained with these compounds with different methods of measuring anxiety (Gargiulo et al. 1996). Starting from this evidence, we could also point out a special concurrent role of these mechanisms in this phenomenon of schizophrenia.

Present task with EA attribution could be applied as a promising neurobehavioral probe for fMRI-studies of pro-psychotic and anti-psychotic brain mechanisms. It could be eventually applied in the everyday clinical practice for subclinical quantitative treatment monitoring, including in clinical trials of novel antipsychotic drugs. Future research with a follow-up (prospective) design would be necessary to verify the feasibility of these theoretical perspectives.

As a cautionary note, the present study is only an initial step within the framework of EA misattribution and has several limitations. One of them is the fact that we have investigated only males, aiming to select more homogenous groups and to prevent the confounding effect of gender. Therefore, future studies that comprise females would be necessary to allow the generalization of our finding.

Another issue is that we have measured only the level of EA subjectively attributed to neutral faces, because we have been particularly concerned with the *subjective* mechanisms of psychotic-symptom formation in patients with paranoid schizophrenia. In future studies it would be worthwhile to compare them with some objective functional-neuroimaging changes during the execution of the task in order to reveal brain mechanisms that underlie the EA misattribution to neutral faces. Furthermore, it would be important to replicate the findings with a longitudinal study.

Future studies could compare the level of EA misattributed to neutral faces in different psychotic syndromes, such as hallucinatory vs. delusional, as well as acute vs. chronic psychoses. 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 EA misattributed to low-arousing/neutral and high-arousing/affective facial expressions in never medicated psychotic patients (before and after treatment) could also provide valuable results.

CONCLUSION

The study provides the first direct empirical evidence for misattribution of emotional salience in terms of over-attribution of EA to neutral faces during acute paranoid schizophrenia psychosis. Theoretically, the neurobiological mechanism behind this EA misattribution might be explained by a deregulated glutamate / dopamine balance transmission leading to a stimulus-inappropriate release of mesolimbic dopamine, which is targeted by the pharmacological antipsychotic treatment. The empirical finding and its explanation suggest that the simple task for EA attribution might be used as a quantifiable marker for psychosis and eventually as a surrogate pharmacodynamic marker for the antipsychotic-treatment effect or psychotogenic drugs experimental effect. Moreover, our finding suggests a new more direct measure for emotional salience misattribution.

Ethical Considerations: Does this study include human subjects? YES

Authors confirmed the compliance with all relevant ethical regulations.

Conflict of interest: No conflict of interest.

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Authors contribution: Dr. Evelina Haralanova has been placed by unanimous decision as the first author of this publication.

Prof. Dr. Emil Milushev has had an important participation both in the interpretation of the results and in the writing of the pertinent conclusions.

The MD, specialist in psychiatry Ángel José Martín Gargiulo contributions to this paper have been highly relevant in the field of neuroscience. His clinical experience has been very relevant in the presentation of these results.

Dr. Mercedes María Lucrecia Gargiulo. Her participation in this paper has been of interest and relevance.

The MD, specialist in psychiatry, Augusto Pascual Ítalo Gargiulo. His topic has been effects of GABA (Gamma-Amino-Butyric Acid) and glutamate antagonists in the ventral striatum. His contributions in this discussion have been very relevant.

MD Marcos Constantino Josué Gargiulo. His contributions to the discussion have been very relevant.

The veterinarian Manuel Guevara. His work has been very relevant to the writing of the discussion of this paper.

Dr. Adrian Inés Landa main contribution in all the works has been experimental design and statistics. In this case, she has also contributed significantly to the writing of the paper, establishing basic-clinical correlations.

Prof. Dr. Norman Darío López Velázquez has contributed in a significant way from his area. His participation in the interpretation of the results has been very significant.

Prof. Dr. José Vicente Lafuente Sánchez. The hypotheses raised in them are the subject of the discussion of this study.

Prof. Dr. Pascual Ángel Gargiulo. The present lines of research represent a continuity of his working hypothesis.

Prof. Dr. Svetlozar Haralanov has contributed in form from the beginning as planner and mastermind of the present study. His contribution has been essential in the design and participation in this study. He has carried out the supervision, as main chairman of the present study. He has been the main intellectual author of the hypothesis of this study. He has been the main designer of the techniques to be deployed. His performance has therefore been central in the interpretation of the results. He has also been artful of the corresponding conclusions.

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