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Neurocognitive deficits or stress overload: Why do individuals with schizophrenia show poor performance in neurocognitive tests?

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ABSTRACT

Poor performance in neurocognitive tasks is consistently found across studies in all stages of schizophrenia spectrum disorders and is interpreted as an underlying, brain function-related, neurocognitive deficit. However, neurocognitive test performance in schizophrenia might be compromised by patients' increased stress level. We investigated group-differences in neurocognitive performance while accounting for psychophysiological (salivary cortisol, heart rate, skin conductance level) and self-reported stress. We included 35 patients with schizophrenia, 29 participants with attenuated psychotic symptoms, 26 first-degree relatives of individuals with schizophrenia and 28 healthy controls. Participants completed a neurocognitive test battery that assessed processing speed, task switching, attention, working memory, verbal episodic memory, and verbal comprehension. Multivariate analyses of covariance (MANCOVA) were calculated to test for main effects of group on neurocognitive performance thereby not accounting versus accounting for confounding effects of stress. As expected, patients with schizophrenia scored lower than the other groups in all neurocognitive domains. Participants with attenuated psychotic symptoms, first-degree relatives and healthy individuals did not differ from each other in their performance. After accounting for heart rate and self-reported stress, the multivariate effect of group on neurocognition remained significant, but was rendered non-significant for specific domains - working memory capacity, episodic memory, and long-term memory. The findings imply that stress is relevant to neurocognitive performance and this should be taken into account when interpreting the origin of performance deficits in schizophrenia patients.

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1. Introduction

Impaired neurocognition has been established as a robust marker of schizophrenia. Across a number of studies, individuals diagnosed with schizophrenia consistently show poor test performance in all neurocognitive domains (Heinrichs and Zakzanis, 1998; Schaefer et al., 2013). In line with previous reviews (Heinrichs and Zakzanis, 1998; Reichenberg and Harvey, 2007), the most recent meta-analysis on neurocognition in schizophrenia yielded moderate to severe effects in all domains and especially large effects in the domains of processing speed and episodic memory (Schaefer et al., 2013). Moreover, impaired neuropsychological test-performance is found in individuals at familial risk for psychosis and first episode patients (Agnew-Blais and Seidman, 2013; Fusar-Poli et al., 2012). The overall pattern of findings has been interpreted as indicative of a global neurocognitive deficit in schizophrenia, with Schaefer et al. (2013) concluding that “the evidence for generalized cognitive impairment in schizophrenia [...] has reached the point of being overwhelming.” (p. 48).

At the same time, neurocognitive performance in general is known to be affected by a variety of factors, including motivation, psychotropic substances or affective states. In particular exposure to stress is known to influence people's performance in cognitive tests (Lupien et al., 2009; Qin et al., 2009). Specifically, it has been found that whereas moderate arousal can be advantageous, performance is likely to decline in the face of high levels of stress (Yerkes-Dodson-Law; Cohen, 2011). Moreover, the effect of stress on performance appears to be particularly strong for tasks involving episodic and long term memory (for an overview see Schwabe et al., 2012; Wolf, 2009) as well as working memory (Lupien, 1999; Oei et al., 2006; Schoofs et al., 2008). Thus, stress is likely to affect neurocognitive performance, especially in domains that tap into different aspects of memory.

Building on the detrimental effects of stress on performance found in healthy populations, it has been hypothesized that chronic stress, such as continuous exposure to noise, is likely to lead to an exacerbation of cognitive deficits in schizophrenia spectrum disorders and might explain the impact of some of the well-known contextual risk factors, such as urbanicity (Wright et al., 2014). Surprisingly, however, there has been a dearth of empirical work examining the interaction between affective components and neurocognitive performance in schizophrenia

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(Burbridge and Barch, 2002, Barch, 2005). In light of the increasingly better understood effects that stress has on neurocognitive performance in general, it seems crucial to account for these effects before drawing conclusions regarding the stability of neuropsychological deficits associated with schizophrenia spectrum disorders. This is especially important considering various studies that have repeatedly found significantly higher stress-levels and stress-sensitivity in patients diagnosed with schizophrenia spectrum disorders (Lardinois et al., 2011; Lataster et al., 2013; Lincoln et al., 2015; Streit et al., 2016) and in individuals at risk (Collip et al., 2011; Palmier-Claus et al., 2012; Reininghaus et al., 2016) than in healthy controls.

This study examines neurocognitive performance in individuals diagnosed with schizophrenia spectrum disorders and those at higher risk of psychosis (first-degree relatives, individuals with attenuated symptoms) while taking into account the effect of psychophysiological and subjective stress on performance. We expected individuals diagnosed with schizophrenia spectrum disorders to show poorer neurocognitive performance than healthy controls across different domains. Moreover, we expected neurocognitive performance to be predicted by the individual's level of stress and examined whether this effect would be moderated by group (i.e. be stronger in patients and risk groups than in healthy controls). Finally, we explored the extent to which the group differences in performance persist after accounting for the level of stress.

2. Methods

2.1. Participants

The sample consisted of 118 participants grouped into four subsamples according to their diagnostic status: 35 participants diagnosed with schizophrenia spectrum disorders (PSY); 29 participants with attenuated positive symptoms (AS); 26 participants with a first degree relative with a schizophrenia spectrum disorder (REL); and 28 healthy controls (HC).

To be included, participants needed to be 18 years or older, have sufficient command of the German language, be able to provide informed consent and have no major neurological disorders. Additional exclusion criteria involved factors that influence the psychophysiological reactions: oral or intravenous medication from the group of steroids, medication that influences cardiac functions or unknown medication, cardiac dysfunctions, as well as smoking, eating or drinking within half an hour prior to testing.

PSY were recruited from in- or outpatient institutions. The mean duration of the disorder in this sample was 13.6 years ($SD = 12.9$). The mean Positive and Negative Syndrome Scale (PANSS; Kay and Fiszbein, 1987) scores were 15.9 ($SD = 4.8$) for the positive syndrome, 14.6 ($SD = 4.2$) for the negative syndrome, and 32.2 ($SD = 6.6$) for the general subscale score. The majority of patients were taking atypical ($n = 20$) or typical antipsychotics ($n = 8$). REL were participants who had a child, parent or sibling with psychotic disorder, recruited from outpatient family intervention services and required not to have past or present psychotic or affective disorder diagnoses. HC and AS were recruited via leaflets, advertisements in local newspapers, and the internet

and prescreened for positive symptoms with the Community Assessment of Psychic Experiences (CAPE; Stefanis et al., 2002). AS were required to reach a cut-off of 1.45 on the positive symptom subscale of the CAPE (based on $M + 1SD$ from two healthy samples reported on in Lincoln et al., 2009; Lincoln et al., 2010). Moreover, at least 50% of the AS sample was required to score above 1.75 ($M + 2SD$). HC were required to have no present Axis I disorder and to score below the cut-off defined for the AS sample. Groups were matched for sex, age and degree of education. A detailed demographical description of participants including their mean CAPE positive subscale scores is provided in Table 1.

2.2. Design and procedure

For the present study, we used data from a randomized repeated measures design where stress was induced in a noise and a psychosocial stress condition. Further details are reported in Lincoln et al. (2015). We used the data acquired at baseline before any stress-induction took place.

2.3. Assessment instruments

2.3.1. Neurocognitive assessment

Processing speed and task switching ability were assessed with the Trail Making Test (TMT; Reitan, 1958). Part A requires connecting numbered circles in an ascending order. In part B numbers and letters are connected in alternating ascending order. Both parts measure processing speed; part B additionally assesses task switching (Rodewald et al., 2012). The score for each task is time to completion. For the analysis, we used IQ-standardized values normed by age on a German population (Rodewald et al., 2012).

Attention was measured by the D2 test (Brickenkamp, 2002). Here, participants are asked to cross out any letter "d" with two marks around, above or below it on a template as fast as possible. Scores are calculated as a difference between the number of correct marks and false marks. Standardized scores were derived based on German age norms. The D2 test has excellent internal consistency with Cronbach's Alpha between 0.95 and 0.98.

Working memory capacity was measured with a digit span (forward) subtest of a German version of the Wechsler Adult Intelligence Scale (WIE; von Aster et al., 2006). We derived IQ-standardized scores based on German population age norms. All subtests of the WIE have a high split-half reliability (Spearman-Brown coefficient: 0.70–0.97).

Episodic memory was measured using the subtest "Story" of the German version of the Rivermead Behavioral Memory Test (RBMT; Beckers et al., 1992). The subtest measures immediate recall of a story content (RBMT-i) and delayed recall after approximately 20 min (RBMT-d). Due to the lack of norms for this subtest we used standardized z-scores for both parts.

The ability to gather, retain and recall general information was measured using the Information subtest of a German version of the WIE (von Aster et al., 2006). The test assesses the degree of general information acquired from culture thereby measuring verbal comprehension and aspects of crystallized intelligence. IQ-standardized scores based on German norms were calculated.

Table 1
Socio-demographic and clinical characteristics of the participants by group.

Variable	Group			
	PSY ($n = 35$)	AS ($n = 29$)	REL ($n = 26$)	HC ($n = 28$)
Age mean (SD)	40.5 (12.5)	35.0 (12.4)	41.7 (13.9)	34.9 (14.4)
Gender in % men/women	58/42	57/43	50/50	62/38
Final school degree in % high/middle/low	46/34/20	82/14/4	75/25/0	62/24/14
CAPE positive subscale mean (SD)	1.89 (0.48)	1.84 (0.27)	1.36 (0.25)	1.28 (0.12)

Note. PSY = participants with schizophrenia spectrum disorders; AS = participants with attenuated positive symptoms; REL = first degree relatives of persons with psychotic symptoms; HC = healthy controls; CAPE = Community Assessment of Psychic Experiences.

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