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## Associations of oxytocin and vasopressin plasma levels with neurocognitive, social cognitive and meta cognitive function in schizophrenia

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### ABSTRACT

Many with schizophrenia experiences deficits in social cognition, neurocognition and metacognition. Yet the biological mechanisms which may underpin these cognitive deficits are poorly understood. Two candidate causes of these deficits are disturbances in oxytocin (OT) and vasopressin (VP). To explore this we assessed plasma OT and VP in 34 schizophrenia patients and 31 healthy controls. We also concurrently assessed social cognition using the Reading the Mind from the Eyes test, neurocognition using the Wisconsin Card Sorting Test and metacognition using the Metacognitive Assessment Scale-Abbreviated. Group comparisons revealed lower plasma OT levels in the schizophrenia group. Plasma VP levels did not differ between groups. Correlations revealed that lower levels of OT were associated with poorer levels of metacognitive functioning in the schizophrenia group but not poorer social cognition or neurocognition. In a stepwise multiple regression, plasma OT level, neurocognition and social cognition contributed uniquely to the prediction of metacognition in the schizophrenia group. Results may suggest that disturbance in OT is linked with deficits in metacognition and may interact with other forms of cognitive deficits, interfering with the person's abilities to form a complex and integrated sense of self and others.

### 1. Introduction

Serious mental illnesses, such as schizophrenia, can lead to widely varying psychosocial outcomes (Leonhardt et al., 2017). Recent studies have suggested that this heterogeneity of outcomes in schizophrenia is a function of the associated features of the illness including disturbances in three related but distinguishable forms of cognition: neurocognition, social cognition and metacognition (Bora et al., 2016; Brüne et al., 2011; Couture et al., 2006; Lysaker and Dimaggio, 2014). Neurocognition refers to the basic set of cognitive processes which allow persons to attend to, remember and organize information within the flow of life. Social cognition, which includes Theory of Mind (ToM), refers to processes which allow people to grasp the meanings of social interactions and mental experiences of others (Bora et al., 2016). Metacognition refers to the most complex of these activities and involves a spectrum of activities which allow persons to have a unique sense of themselves and others available in the moment in response to emerging demands of life

(Lysaker et al., press; Lysaker and Klion, 2017; Semerari et al., 2003). Although metacognition has been referred to as an element of social cognition (Pinkham, 2014), the two constructs differ in that social cognition refers to the accuracy of social judgements, while metacognition is concerned with integration and complexity and represents higher order or cross contextual judgements about the self and other. Qualitative the constructs also differ in that social cognition seems to be more related to accuracy in perception while metacognition is related to ongoing abilities of creating integrative representations. Also social cognition is more automatic and less purposefully reflective. In this sense evidence for the independence between social and metacognition has also been demonstrated in factor analyses (Lysaker et al., 2013) and cross-sectional studies (Hasson-Ohayon et al., 2015).

To date, it remains unclear what underlying biological processes are responsible for the emergence and persistence of these difficulties in cognition and how these forms of cognition and underlying biological processes interact with one another. A better understanding of these

*Abbreviations:* WCST, Wisconsin Card Sorting Test; RMET, Reading The Mind From The Eyes Test; MAS-A, Metacognition Assessment Scale-Abbreviated; IPII, The Indiana Psychiatric Illness Interview; OT, Oxytocin; VP, Vasopressin; ToM, Theory of Mind

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processes could influence the development of novel biological treatments for these disturbances, allowing for greater opportunities for recovery, particularly with regard to psychosocial functioning. Accordingly, the current study explored: i) whether levels of neurocognitive, social cognitive and metacognitive function among a group of patients with schizophrenia were differentially related to oxytocin (OT) and vasopressin (VP), and ii) whether relationships between complex patterns of biological processes and more basic cognitive processes could be detected as these could interfere with higher order cognitive processes.

OT and VP are neuropeptide hormones that are produced by the hypothalamus and secreted by the posterior pituitary gland. The OT and VP genes are both located on chromosome 20 and their structure differs by only a couple of amino acids, suggesting an evolutionary and functional relation (Gimpl and Fahrenholz, 2001). There are several reasons to believe OT and VP may contribute to disturbances in neurocognition, social cognition and metacognition. In the central nervous system, they act on multiple brain regions as neuromodulators and influence a range of neurophysiological processes and behaviors (Stoop, 2012). OT has been suggested to modulate multiple social cognitive domains related to trust, attachment behavior, stress response, social memory, and the ability to recognize emotions and understand mental states (Gumley et al., 2014; Meyer-Lindenberg et al., 2011). VP has also been suggested to influence various forms of cognition, including social cognition, non-spatial memory, and attention (Caldwell et al., 2008). Intranasal OT has also been found to improve performance in social cognitive tasks related to the perception of sarcasm, deception, and empathy (Davis et al., 2013) and the results have been replicated using a placebo group (Davis et al., 2014). The disruptions in peripheral levels of VP have been linked to poorer cognitive functioning (Rubin et al., 2013).

In this study we tested two primary hypothesis: (1) schizophrenia patients would show differences in plasma OT and VP levels compared to non-psychiatric controls, and (2) differences in OT or VP would be related to deficits in one form of neurocognition (i.e., executive function), one form of social cognition (i.e., ToM) and metacognition in patients with schizophrenia and that differences in OT or VP would be related to deficits in one form of neurocognition (i.e., executive function), and one form of social cognition (i.e., ToM) in health controls.

We also tested an exploratory hypothesis, that disturbances in OT and VP, deficits in executive function and ToM would uniquely predict disturbances in higher order cognitions about self and other (i.e., metacognition). Here we were interested in exploring the extent to which biologically based processes and lower order cognitive processes contribute to the broader cognitive processes which require higher levels of integration. We reasoned that while biological processes (OT or VP) might be related to both neurocognition and social cognition, their effect on metacognition might be independent of one another. For example, if executive function and ToM provide information which serve as building blocks for metacognitive activities, then deficits in each might leave persons with metaphorically fewer raw materials to be

synthesized into complex ideas of the self or others, resulting in more impoverished metacognition. This is consistent with studies suggesting that certain forms of metacognition, social cognition and neurocognition are linked to each other and these cognitive functions affect social functioning in schizophrenia (Lysaker et al., 2010a, 2010b; Schmidt et al., 2011).

## 2. Material and methods

### 2.1. Participants

Two groups of research participants took part in the present study. The patient group included 40 persons with a diagnosis of schizophrenia being treated in the psychiatric unit of Celal Bayar University. The patients met DSM-IV-TR criteria for schizophrenia as determined by medical records and diagnosis was confirmed with the Structured Clinical Interview for DSM-IV – Patient Edition (SCID) (First et al., 2002). Inclusion criteria included clinical stability as defined by no change in medication dosage in the last three months, and no hospitalization in the last 6 months before recruitment for the study. For both groups, exclusion criteria were the presence of a substance use disorder, mental retardation, dementia and being older than 65 years (in order to avoid possible confounders of cognitive deficits due to aging), use of hormone treatments, experiencing menstration, and hospitalization and pregnancy/lactation within the last year. All patients with schizophrenia received second-generation antipsychotic medications. Mean chlorpromazine equivalent dosages (CPZ) were  $528.14 \pm 318.67$  mg per day (Rijcken et al., 2003). The non-psychiatric group consisted of 38 persons who did not have a psychiatric diagnosis based on clinical interviews completed by two different experienced psychiatrists. Participants were instructed to abstain from caffeine and nicotine on the day of the study and from food or drinks other than water in the 2 hours prior to participation. The blood samples were collected between 8 am and 9 am, and all of the performance tests were conducted within the same day. Demographic characteristics of the participants for each group are presented in Table 1. All participants provided written informed consent. The study was approved by the local Institutional Review Board.

### 2.2. Instruments

#### 2.2.1. The Wisconsin Card Sorting Test (WCST)

The Wisconsin Card Sorting Test (WCST) has often been cited as the most frequently used measure of executive functioning (Baddeley and Della Sala, 1996; Barceló and Knight, 2002; Heaton, 1993; Stuss and Levine, 2002) and is regularly used by over 70% of neuropsychologists (Butler et al., 1992). The computerized version of the WCST consists of 4 “Cards” shown on the computer screen distinguished by the form, number, and the patterns found on each card. The participant selected a target card that matched a given trial card according to one feature. After the participant correctly matched the cards in 10 consecutive

**Table 1**  
Comparison of characteristics between the two groups.

	Group						Stats.
	Schizophrenia (n = 34)			Healthy (n = 31)			
	Mean	S.D.	Count (%)	Mean	S.D.	Count (%)	
Age	30.05	7.41		29.67	7.19		$t(63) = 0.210, p = 0.83$
Gender							
Male			22(64%)			13(41%)	$\chi^2(1) = 3.83, p = 0.08$
Female			12(36%)			18(59%)	
Education(years)	10.44	3.09		11.45	3.50		$t(63) = -1.23, p = 0.22$
Duration of illness(years)	10.55	7.22					
Disease onset age	19.52	3.87					

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