Aus der Klinik für Psychiatrie und Psychotherapie
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DISSERTATION

„Endogenes Oxytocin bei Patient*innen mit Schizophrenie - Veränderungen der Plasma-Oxytocinkonzentration in Reaktion auf emotionale Filmstimuli und Zusammenhänge mit dem empathischen Erleben im Vergleich zu Gesunden“

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1. **Abstracts**

1.1. Abstract Deutsch

Hintergrund: Oxytocin ist ein Hormon, das eng mit der sozialen Funktion und dem Bindungsverhalten des Menschen verbunden ist. Bei Störungen mit eingeschränkter sozialer Kognition und Empathie wurden Anomalien im oxytocinergen System nachgewiesen, und seine Verwendung als Therapeutikum hat ein gewisses Potenzial zur Verringerung von Symptomen, z. B. bei Patient*innen mit Psychosen, gezeigt. Gleichzeitig gibt es erste Hinweise darauf, dass die endogene Oxytocinsekretion im Zuge emotionaler Interaktionen in dieser Patient*innengruppe verändert sein könnte. In dieser Studie verwendeten wir emotionale Kinderfilme, um die endogene Oxytocinsekretion bei Patienten mit Schizophrenie und gesunden Kontrollpersonen zu stimulieren und zu vergleichen. Wir beschreiben darüber hinaus Assoziationen der Oxytocin-Reaktivität mit Parametern für Empathie, Bindungsstil (Psychosis Attachment Measure - PAM), Kindheitstrauma (Childhood Trauma Questionnaire – CTQ) und Psychopathologie (Positive und Negative Syndrom Scale - PANSS).

Methoden: Wir rekrutierten 35 Patient*innen mit Schizophrenie und 35 gematchte gesunde Kontrollpersonen und verwendeten drei emotionale Kinderfilme, in denen Szenen von Bindung und Verlust dargestellt sind, um die Oxytocinsekretion zu stimulieren. Die Messung erfolgte durch Entnahme von Blutproben in einer peripheren Vene. Wir verwendeten einen Radioimmunoassay mit sog. pre-assay sample extraction, um die Oxytocin-Plasmaspiegel vor und nach dem Betrachten von Filmszenen zu bestimmen. Die Ergebnisse wurden mit denen einer Kontrollbedingung verglichen die eine Wetterdokumentation zeigte.

Ergebnisse: Wir fanden bei weiblichen Patientinnen im Vergleich zu allen anderen Gruppen niedrigere Oxytocin-Ausgangswerte. Die Oxytocin-Reaktivität während emotionaler Filme war bei Patient*innen im Vergleich zu Kontrollen signifikant höher, wobei dieser Effekt bei weiblichen Patientinnen am stärksten ausgeprägt war. Wir

fanden keinen Zusammenhang zwischen den Oxytocin-Ausgangswerten bzw. Oxytocin-Reaktivität und PANSS-, CTQ- oder PAM-Scores.

Schlussfolgerung: Unsere Studie beschreibt signifikante geschlechtsabhängige Unterschiede in den Oxytocin-Ausgangswerten und der Oxytocin-Reaktivität gegenüber einem emotionalen Filmstimulus zwischen Patient*innen mit Schizophrenie und gesunden Kontrollpersonen. Dies legt nahe, dass Oxytocin ein geschlechts- und kontextabhängiger Modulator sozio-emotionaler Prozesse bei Schizophrenie ist.

1.2. Abstract English

Background: Oxytocin is a hormone that has been intricately linked with social functioning and attachment in humans. In disorders with impaired social cognition and empathy, abnormalities in the oxytocinergic system have been demonstrated, and its use as a therapeutic agent has shown some potential in reduction of symptoms, e.g. in psychosis. At the same time, there is evidence that endogenous oxytocin secretion may be altered in the context of emotional interactions in this patient group. In this study, we used emotional children's movies to stimulate and compare endogenous oxytocin secretion in patients with schizophrenia and healthy controls. We describe associations of oxytocin reactivity with measures of empathy, attachment style (Psychosis Attachment Measure), childhood trauma (Childhood Trauma Questionnaire) and psychopathology (Positive and Negative Syndrome Scale – PANSS).

Methods: We recruited 35 patients with schizophrenia and 35 matched healthy controls and used three emotional children's movies portraying scenes of bonding and loss to stimulate oxytocin secretion. Measurement was done by collection of blood samples in a peripheral vein. We used radioimmunoassay with sample extraction to determine oxytocin plasma levels before and after viewing of movie scenes. Results were compared with those of a control condition showing a weather documentary.

Results: We found lower baseline oxytocin levels in female patients compared to all other groups. Oxytocin reactivity during emotional movies was significantly higher in patients compared to controls, this effect being most prominent in female patients. We found no association of oxytocin baseline levels or oxytocin reactivity to PANSS, attachment style or childhood adversity scores.

Conclusion: Our study describes significant gender-dependent differences in oxytocin baseline levels and oxytocin reactivity to an emotional film stimulus between patients with schizophrenia and healthy controls. This suggests oxytocin to be a gender- and context-dependent modulator of socio-emotional processes in schizophrenia.

2. Manteltext

2.1. Introduction

Schizophrenia is a multifactorial psychiatric illness that affects approximately 1% of the global population. Patients suffer from significant alterations in thought processes, mood and behavior, and core symptoms can be broadly categorized as so called positive or negative symptoms. Typical positive symptoms are hallucinations, delusions, and distortions of self-experience, while negative symptoms can be lack of motivation, apathy, social withdrawal, inability to feel pleasure, among others. More importantly, though, patients experience impairments in their everyday functioning, e.g. vocational and leisure functioning, maintenance of interpersonal relationships and independent living. Especially negative symptoms can lead to major disturbances in functional outcomes, as they are related to deficits in self-care and social isolation (Ventura et al., 2009). Additionally, functional outcomes appear to be strongly dependent on cognitive impairment in schizophrenia (Green et al., 2000).

Recently, social cognitive impairments have been recognized as a major determinant of functional outcomes in schizophrenia, as evidence suggests it plays an even bigger role than negative symptoms and non-social aspects of neurocognition (Fett et al., 2011; Maat et al., 2012). Moreover, social cognition deficits are a center-piece of social exclusion in schizophrenia (Yager and Ehmann, 2006).

The NIMH (National Institute of Mental Health) initiative has described the research field of social cognition in schizophrenia as having five domains: emotion processing, social perception, social knowledge, theory of mind, and attributional biases (Green and Leitman, 2008). Of note, empathy as a distinct entity is not mentioned. Theory of Mind, the ability to infer others' mental states, partially overlaps with the definition of cognitive empathy (see below) and may be involved in the emergence of delusion in schizophrenia (Frith, 2004). It has also been shown to be a strong predictor of poor quality of life in schizophrenia patients (Maat et al., 2012). However, Theory of Mind does not refer to the emotional aspects of empathy. Social cognition is closely related to emotion and affective ability, recruiting similar suites of cortical and subcortical

neural systems, and it has been suggested that they represent intertwined aspects of the same phenomenon (Olsson and Ochsner, 2008). However, emotional aspects of social cognition, such as affective empathy, although decisive for functioning of interpersonal processes, have not been sufficiently studied in schizophrenia and related disorders.

Empathy in schizophrenia

Empathy as a general concept can be described as the ability to recognize, understand, and vicariously feel the emotions of others (De Vignemont and Singer, 2006), and can be thought of as a multidimensional construct (Davis, 1983). Its components are not uniformly described in scientific literature, but generally two main aspects can be discerned: cognitive empathy (which is conceptualized as the ability of perspective taking and to recognize and understand others' feelings) and affective empathy (the ability to experience the same or similar, "isomorphic" emotions (Walter, 2012) as others). Furthermore, empathy is closely related to broader aspects of social behavior, such as prosocial responses (Davis, 1983; Piliavin and Charng, 1990).

While a vast body of literature describes significant deficits in cognitive empathy in schizophrenia (Brüne, 2005; Derntl et al., 2009; Achim et al., 2011), its effects on affective empathy are still not well understood (Derntl et al., 2012). A recent metanalysis revealed significant deficits in affective empathy (Bonfils et al., 2016), but describing patients' emotional response to others' feelings as diminished or simply "blunted" is not painting the full picture. For instance, schizophrenia patients seem to experience more personal distress when confronted with emotional stressors (Bonfils et al., 2017). Achim et al suggests that the disease leads to impaired emotion regulation mechanisms, rather than an overall affective empathy impairment (Achim et al., 2011).

Oxytocin

Oxytocin is a hormone and neurotransmitter which has gained attention in recent years. It is synthesized in the hypothalamus and from there it can be transported via neural axons to serve as a neurotransmitter, or it may be released from cell bodies

acting as a paracrine signal, but both release variants are restricted to neural pathways in their effects. Alternatively, after being synthesized, oxytocin is transported to the hypophysis and from there released into the bloodstream. From there, it can act as a peripheral hormone. For a more in-depth review see (MacDonald and MacDonald, 2010).

Apart from its undisputed role in sexual behavior (Burri et al., 2008), birth, lactation, child rearing (Uvnäs-Moberg et al., 2001; Carter, 2003; Feldman et al., 2007; Augustine et al., 2018), and attachment (Carter, 1998; Insel and Young, 2001; Buchheim et al., 2009), its modulatory role has been shown in a variety of human psychosocial aspects. It is generally regarded as an important modulator of social cognition and empathy (Domes et al., 2007b; Bartz et al., 2011), was shown to improve “mind reading” (interpreting mental state from facial gestures) (Domes et al., 2007b; Fischer-Shofty et al., 2010), cooperation (De Dreu and Kret, 2016), trust and trustworthiness (Kosfeld et al., 2005; Zak et al., 2005), and to regulate fear (Kirsch et al., 2005) and distress during social interaction (Gimpl and Fahrenholz, 2001; Onaka, 2004; Uvnäs-Moberg and Petersson, 2005; Pierrehumbert et al., 2010). For more details see (MacDonald and MacDonald, 2010; Hurlemann and Scheele, 2016).

Oxytocin has been suggested to condition intergroup relations, acting on mesocorticolimbic circuitry to promote social approach, but also on cortico-amygdala circuitry, reducing withdrawal from social threat, increasing vigilance, and even promoting aggressive responses to social threat, especially to offspring (De Dreu and Kret, 2016). Thus, oxytocin effects are not exclusively prosocial, as it may trigger behavior evolutionarily related to offspring survival, and, while promoting in-group bonding and cooperation, may consequently lead to out-group ostracism (De Dreu and Kret, 2016; Hurlemann and Scheele, 2016). Its effects on experience and interpretation of social cues may be dependent on personal variables (i.e. sex, attachment style, early-life experiences, presence of psychiatric symptoms, etc.) as well as context (e.g. perception of others as friend or foe) (Bartz et al., 2011; Olff et al., 2013). Additionally, it has been suggested that oxytocin induces a self-referential processing bias, increasing interoception awareness, hereby promoting conscious representation of emotional experiences (Hurlemann and Scheele, 2016).

Oxytocin also acts as a stress and anxiety buffer when social support is present but can also elevate social stress in its absence. Loss of affectionate bonds have been suggested to disrupt oxytocin signaling and as a consequence, contribute to emotional disequilibrium (Hurlemann and Scheele, 2016). In the context of social threat, oxytocin secretion may also be related to increases in anxiety and distress, in order to motivate coping attempts (Crespi, 2016). Due to negative feedback regulation, oxytocin levels may decline following resolution of social challenges. If these challenges cannot be resolved, continuously elevated oxytocin levels might further support social vigilance and mentalizing (Crespi, 2016).

Moreover, early life experiences significantly moderate oxytocin effects (Feldman, 2017). Disruption of early-life bonds and relationships, especially in the context of trauma and abuse, is associated with lower oxytocin levels (Heim et al., 2009), social withdrawal, atypical social behavior and vulnerability to psychiatric illness (Fox et al., 2017). Attachment, the human need to form and maintain interpersonal relationships, is highly dependent on early life experiences (Ahern and Young, 2009; Rincón-Cortés and Sullivan, 2014), and appears to have a significant role in the regulation of oxytocin response (Rilling, 2009). In persons with psychotic disorders and schizophrenia, attachment styles have been found to be insecure more frequently compared to healthy individuals (Berry et al., 2006), and early adversity has been acknowledged to considerably contribute to psychosis risk (Varese et al., 2012). Moreover, attachment style is closely related to interpersonal functioning (Berry et al., 2006), has been linked with social cognition in clinical samples (Venta et al., 2017) and with symptom severity in psychotic disorders (Berry et al., 2008).

Oxytocin system abnormalities might therefore relate to psychotic vulnerability by dysregulation of attachment, social approach and unsatisfactory interaction experience on one hand and disturbed mentalizing capacity, hypervigilance and perception of aberrant salience and social threat on the other (Crespi, 2016; Debbané et al., 2016).

Moreover, oxytocin also seems to regulate central dopamine pathways. Given dopamine's significance in the pathophysiology of schizophrenia, some authors have suggested that oxytocin's possible therapeutic effects may in part be explained by its interaction with the dopaminergic system (Meyer-Lindenberg et al., 2011; Rosenfeld et

al., 2011). Further, it has been suggested that anomalous responses to emotional stimuli in schizophrenia may be mediated by dysfunctions in the amygdala-dopamine-oxytocin neurocircuitry (Rosenfeld et al., 2011).

Lastly, concerning oxytocin's presumed involvement in disease vulnerability in schizophrenia, there is some evidence suggesting the presence of certain oxytocin receptor variants to be associated with both higher risk of developing schizophrenia and higher symptom severity (Souza et al., 2010; Montag et al., 2013), as well as social cognition in schizophrenia (Davis et al., 2014).

Many trials have therefore focused on oxytocin as a treatment strategy in disorders characterized by deficits in social abilities, such as autism, post-traumatic stress disorder, mood disorders, borderline personality disorder and of course, schizophrenia. Unfortunately, meta-analyses of randomized, double blinded trials found no significant effects of oxytocin as a therapeutic agent on negative, positive or general psychopathology in schizophrenia (Oya et al., 2016; Williams and Bürkner, 2017; Zheng et al., 2019), except in high dose therapy subgroups (80 IU/day), where a significant effect on symptom severity was described (Oya et al., 2016; Zheng et al., 2019).

Furthermore, while oxytocin's role as a therapeutic agent is heavily discussed, little is known about the regulation of endogenous oxytocin in schizophrenia. Current evidence on baseline oxytocin levels in schizophrenia is inconclusive, describing either lower levels than healthy controls (Goldman et al., 2008; Jobst et al., 2014; Aydın et al., 2018), increased levels (Walss-Bass et al., 2013; Strauss et al., 2015c), or no significant differences (Rubin et al., 2010, 2014).

Studies relating endogenous oxytocin levels to schizophrenia symptom severity have yielded mixed results (Legros et al., 1992; Goldman et al., 2008; Keri et al., 2009; Rubin et al., 2010; Sasayama et al., 2012; Rubin et al., 2017), but predominantly point to an association of more severe symptoms with lower endogenous oxytocin levels, which might be gender-biased (Rubin et al., 2010, 2017).

Higher oxytocin plasma levels in schizophrenia patients seem to predict better recognition of social cues (Strauss et al., 2015a) and facial emotions (Goldman et al., 2008), less asociality (Strauss et al., 2015b), and overall better neuro- and social

cognitive abilities (Frost et al., 2014). Additionally, higher oxytocin plasma levels have been related to more precise recognition of emotions in both schizophrenia patients and healthy controls, this effect being most prominent in female patients (Strauss et al., 2015c). However, emotion recognition effects might also be biased, as higher endogenous oxytocin levels are associated with the recognition of faces as happier (Rubin et al., 2011). This effect was also seen only in female patients and controls, not in men.

Generally, it has been suggested that stimulus-evoked oxytocin level changes could be more reliable than measurements of non-induced baseline concentrations, as these seem highly variable (Zak et al., 2005; Kéri and Kiss, 2011). In a schizophrenia sample, oxytocin release during a trust-related task also seemed to be blunted in patients with more severe negative symptoms (Keri et al., 2009), but to our knowledge, there is only one study on oxytocin level changes following emotional stimuli in this disorder.

For this reason, we decided to use a video-based stimulation protocol to determine induced oxytocin level changes in addition to baseline oxytocin levels in a sample of patients with paranoid schizophrenia. Video stimuli were chosen to depict interpersonal scenes of attachment and loss to induce empathy with the main character, as emotional responses to the respective interpersonal situations were deemed to be highly relevant in the manifestation and treatment of patients with this disorder. Aim of this pilot study was to explore baseline levels and the video-induced reactivity of the endogenous oxytocin system, measured as plasma oxytocin, in patients with schizophrenia and to compare it to healthy controls. Moreover, oxytocin measures should be related to parameters of attachment, early adversity and behavioral empathic abilities.

On an exploratory basis, we hypothesized that schizophrenia patients would (i) differ in oxytocin baseline levels when compared to controls, (ii) show reduced oxytocin reactivity following an emotional stimulus, and (iii) show an association between oxytocin (baseline levels and reactivity) and both history of childhood trauma and attachment style. Further, it was hypothesized that (iv) oxytocin baseline levels and oxytocin reactivity would be associated with cognitive and emotional empathy, and that these associations would differ between schizophrenia patients and healthy controls.

2.2. Methods

Participants

The study was approved by the institutional review board ("Ethics Committee") of the Charité—Universitätsmedizin Berlin. We recruited in- and out-patients with paranoid schizophrenia, according to DSM-IV-TR, aged 18-65, of the Charité Psychiatric University Clinic at St. Hedwig Hospital in Berlin. Diagnosis was confirmed by trained psychiatrists using the structured clinic interview for DSM-IV (SCID I and II, German versions, Wittchen et al., 1997). Symptom severity was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), as well as the Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS) (Andreasen, 1984a, 1984b) (see table 1 of Speck et al., 2019).

Healthy controls were recruited by printed advertisements and direct verbal advertisement in the hospital and university. Controls were screened with structured interviews (MINI, Sheehan et al., 1998, SCID II).

All subjects gave informed written consent and were paid 40 Euros for their participation. We asked subjects to abstain from alcohol and cannabis consumption 24 hours prior to testing. Subjects that reported consuming these substances in this time frame were excluded from the analysis. Exclusion criteria for both groups were DSM-IV axis-I or axis-II mental disorders (except schizophrenia for the patient group), acute suicidality, organic brain disease and current substance abuse. Controls reporting axis-I or -II mental disorders, as well as DSM-IV axis-I disorders in their first- or second-degree relatives were excluded.

Discussion on oxytocin measurement assays

There has been much debate about the most precise and reliable method of oxytocin measurement in recent years. In current studies, three main methods are described: Radioimmunoassay (RIA), developed in the 1980s, the newer Enzyme Linked-Immunosorbent Assay (ELISA), and mass spectrometry (MacLean et al., 2019). Many studies on oxytocin have now used ELISA for analysis, as RIA is often more cost-intensive (it requires special precautions and expensive equipment because of

hazardous radioactive materials and short half-lives of isotopes). However, RIA delivers physiologically plausible results and has been described as the gold standard for measuring peripheral oxytocin by some authors (Lefevre et al., 2017). Mass spectrometry is a fairly recent method of oxytocin measurement, but has been used by some teams and has yielded plausible results (Lefevre et al., 2017). Other analysis methods like estimation derived from indirect oxytocin measurement have also been reported in older literature, but have produced largely different results, with levels up to 1000 times higher than usually described in studies using RIA with sample extraction (Legros et al., 1992).

Assay specificity can be further improved by using an extraction process to remove irrelevant proteins that might interfere with testing. Not using the extraction method alone can change results from the usual 1-10 pg/ml with extraction to more than 300 pg/ml (Szeto et al., 2011).

Studies comparing different analytic procedures have delivered sobering results, with some not even finding evidence of inter-assay correlation (Lefevre et al., 2017). However, it has been suggested that discrepancies between methods are still not well understood, possibly indicating that different states of the same molecule are being measured, and that it is premature to set a general standard for measurement method (MacLean et al., 2019).

We conducted our analysis in cooperation with a laboratory using RIA with pre-assay sample extraction (Prof. Dr Rainer Landgraf, RIAgnosis, Munich; http://www.riagnosis.com), a combination considered to be the most reliable and best-validated (Szeto et al., 2011; Neumann et al., 2013; McCullough et al., 2013; Christensen et al., 2014; Lefevre et al., 2017). Our results are consistent with described human baseline oxytocin levels in literature using this method.

Stimulating the oxytocinergic system with emotional films

To evoke empathic feelings and oxytocin release, different approaches have been made, but it seems one of humans' most early experiences in life is being overlooked: children's movies. While these movies are often colorful, filled with musical background

and comedic characters, many of them portray a great social loss during the plot. One of the most classic examples is the movie “Bambi” (Hand, 1942), where the young deer’s mother is shot to death and he is left alone, facing the challenges of living in the woods by himself. Such emotionally laden scenes serve the purpose of making the viewer empathize with the main character. We opted for showing selected scenes from three children movies (see below), each sequentially portraying both interpersonal bonding between characters and death of one of the characters.

Film protocol

Subjects were randomly assigned to do either a test version where the emotional films were shown before the control film (test version 1) or a version that begins with the control film (test version 2).

The scenes (5 min, 44s for “Lion King”, Allers and Minkoff, 1994; 6 min, 37s for “Bambi”, Hand, 1942, 4 min, 21 s for “UP!”, Docter, 2009), were always shown consecutively and in the same order. As a control condition, we chose a scene from a weather documentary (3 min, 37s) (Komplett-Media, 2004), featuring a narrator talking about different weather phenomena. The scene could be described as monotone and emotionless in its mood, focusing on how different temperatures in same latitudes are possible and how oceans and topography affect temperature changes.

After showing each emotional film cut, we asked participants “how strongly did you feel with the main character throughout the movie?” (EMPATHY), “how much have you felt stressed or fearful?” (STRESS) and “how relevant is this scene in your life?” (RELEVANCE). Subjects were asked to give their answer on a scale of 1 to 6.

After showing the control film, the first question, “how strongly did you feel with the main character throughout the movie?”, was replaced with “how relaxed were you during the film?” (RELAXATION) since the short documentary featured no main character. The following two questions were the same as in the emotional films.

Psychometric measures

In addition to measuring oxytocin, we conducted a series of behavioral tests, allowing us to further contextualize our results.

As measures of cognitive and affective empathy, we used the Multifaceted Empathy test (MET) (Dziobek et al., 2008) and a German version of the Interpersonal Reactivity Index (IRI) (Paulus, 2009). The MET is a picture-based test, where the subject is sequentially confronted with 40 photographs of people in emotionally charged situations, depicting both positive and negative emotions. Subjects are required to infer the depicted emotion ("How does this person feel") by picking from four given alternatives. This is a measure of cognitive empathy. Subjects are then asked to rate their own isomorphic emotional response to the image ("How strongly did you feel the same emotion like the person in the photograph?") on a scale of 0-9, which can be seen as a measure of emotional empathy. The test has demonstrated to be useful in evaluating empathic abilities in schizophrenia samples (Lehmann et al., 2014), and is not restricted to isolated facial emotional recognition, but rather relies on depicting subjects in emotionally charged situations, allowing for higher ecological validity (Dziobek et al., 2008).

The IRI conceptualizes empathy as a four-dimensional construct, consisting of perspective taking, fantasy, empathic concern, and personal distress. Perspective taking is the ability to understand and adopt others' point of view and to reason about their mental states. Its definition partially overlaps with the definition of cognitive empathy. Fantasy refers to identifying with fictional characters in movies, books, etc... Empathic concern is defined as the tendency to feel concern, warmth, and sympathy towards others. Finally, personal distress refers to feelings of anxiety and discomfort in response to seeing the distress of others. The IRI is a 25-item self-rating questionnaire, each item being rated on a 5-point Likert scale.

Additionally, we applied German versions of the short form of the Childhood Trauma Questionnaire (CTQ) (Klinitzke et al., 2012) and the Psychosis Attachment Measure (PAM) (Berry et al., 2006). With the permission of K. Berry, the test author, we translated PAM to German using the back-translation method.

The short form of the Childhood Trauma Questionnaire, originally published in 2003 (Bernstein et al., 2003), is a screening instrument internationally used to assess experiences of abuse during childhood. It consists of 28 questions, divided in three

categories: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. It has been well validated in community and clinical samples.
PAM is a 16-item questionnaire designed to assess insecure attachment forms. It is a measurement of two insecure attachment dimensions: anxiety and avoidance.
The multiple choice vocabulary test (Mehrfachwahlwortschatztest, MWT-B) (Brickenkamp and Brähler, 2002) and a German version of the Auditory Verbal Learning Test (AVLT – first five presentations were used for analysis) (Heubrock, 1992) were used as measures of general cognitive function, attention, vocabulary knowledge and verbal learning.

Procedure

All subjects were tested between 10:00 and 13:00 hours. First, an 18-gauge peripheral venous catheter was placed on the subjects' forearm or backhand by one of the phlebotomy-trained investigators. Whenever possible, we chose the cephalic vein or basilic vein, as these are more likely to produce blood back-flush due to their bigger diameter, allowing for blood samples to be collected easily without inflicting further pain to the subject.
The patient was brought into a testing room, where a computer was set up. To alleviate the stress of venipuncture, we waited at least 10 minutes before continuing testing. Next, we showed the emotional film sequence (test version 1) or the control film (test version 2) on the computer screen (17 inches, about 1-meter distance to screen, moderately bright room). After each short film, three questions were presented to the subject (described above), his answers were noted. We gave subjects 60 minutes between both film conditions, to allow enough time for a theoretical spike in oxytocin levels to return to (or close to) baseline, as has been described in previous studies (Krüger et al., 2006). Neurocognitive testing was done in this time slot. After both film conditions, psychometric testing followed (PAM, IRI and MET).
Before the first and 1 minute after the last emotional film, as well as before and 1 minute after the weather documentary, blood samples were collected and transferred to a citrate vacuum tube. In total, 4 citrate samples were collected from each subject. Samples were placed in a refrigerated container (-18°C) immediately after collection

and transported to the clinic lab immediately after testing, where they were centrifuged and frozen (-28°C) in Eppendorf vessels containing exactly 0.8 ml of serum. Oxytocin concentrations were determined by radioimmunoassay using solid phase sample extraction. Testing was done by Prof. Dr. Rainer Landgraf, RIAgnosis, Munich (http://www.riagnosis.com). Assay sensitivity for this method is in the 0.1 pg/ml sample range, intra- and inter-assay variability is under 10% and no significant cross-reactivity is reported. Testing details such as extraction and analysis methods as well as validation are reported in (Neumann et al., 2013).

Statistical analysis

We analyzed the data using IBM SPSS Statistics 22. Normal distribution was assessed with the Kolmogorov-Smirnov test. As a measure of oxytocin reactivity, we calculated the ratio of oxytocin change for both the emotional condition (EC) and control condition (CC):

$$EC\ reactivity\ = \frac{Oxytocin\ after\ EC\ films}{Oxytocin\ before\ EC\ films}$$

$$CC\ reactivity\ = \frac{Oxytocin\ after\ control\ films}{Oxytocin\ before\ control\ films}$$

To obtain normal distribution we performed a logarithmic transformation (logarithm base 2). Of note, the base of the logarithm has no mathematical relevance to the statistical results:

$$ECreact = log_2(EC\ reactivity)$$

$$CCreact = log_2\ (CC\ reactivity)$$

Reference for all four equations: Speck et al., 2019

2.3. Results

Detailed results have been reported in our two published papers (Speck et al., 2019; Montag et al., 2020b).

In total, we recruited 42 patients with paranoid schizophrenia and 39 healthy controls. Hormone levels of 6 patients could not be analyzed because either 1 or more blood samples coagulated before centrifugation, or blood collection in the aforementioned time frame failed. Data for these subjects was discarded. One patient showed non-detectable baseline blood oxytocin levels (<0,005 pg/ml) and was therefore excluded from the analysis, as values <0.06 pg/ml in the RIA with sample extraction are considered not valid (Christensen et al., 2014). We used age and gender to match 35 healthy controls to the patient group. In total, data for 70 subjects was analyzed, 35 patients and 35 healthy controls.

See table 1 in our first publication (Speck et al., 2019) for a comprehensive overview of the socio-demographic data. For verbal IQ, there were 2 missing values. They were substituted by the group mean. For three patients, psychopathological measures (PANSS, SAPS/SANS) could not be assessed.

For female subjects, we noted the menstrual cycle phase based on the timeframe of their last menses. Coded as menses/follicular/luteal/menopause/unknown, distribution was n = 2/2/5/1/2 in the patient group, and n = 0/2/3/2/5 in healthy controls (χ^2 = 4.119, P = 0.390).

Baseline oxytocin levels

To assess baseline oxytocin levels before the experiment we collected blood samples before showing the first video. Baseline levels were not significantly different in patients and controls, as assessed by Mann-Whitney U test. Subsample analysis of males and females revealed significantly lower oxytocin levels in female patients compared to female controls. There was no significant difference in the males' subsample. See results in table 3 of (Speck et al., 2019).

We also conducted a Spearman rank-order correlation (separate analysis of controls and patients) to assess the relationship between baseline oxytocin levels and socio-

demographic characteristics. We did not find any significant correlation of baseline oxytocin with age, verbal IQ, Auditory-Verbal Learning Test (AVLT), schooling and training years or highest educational level.
Results on oxytocin baseline and sociodemographic correlations have been published in (Speck et al., 2019).

Self-reported film responses

We found no significant group differences for EMPATHY, AROUSAL or subjective RELEVANCE scores in the emotional condition. However, schizophrenia patients showed significantly lower self-rated RELAXATION and higher AROUSAL values during the control film than healthy controls.
As evidenced by qualitative debriefing after showing of the three emotional scenes, subjects experienced a variety of emotional responses. We categorized accounts to objectify our movies' emotional effects (schizophrenia patients/healthy controls – subjects could only be allocated to one category). Some reported feeling a fear of loss and/or of longing for attachment (14/10), others gave emotional personal (5/10) or impersonal (2/7) recollections. Interestingly, only schizophrenia patients (5) reported feelings of loneliness. Of note, a minority of subjects gave emotionally detached, rational accounts (4/1) and one subject refused to answer (1/0). As we asked open ended questions, some answers could not be allocated to one of the above categories. As some of our study subjects described, the scenes in question often reminded them of their own past, be it growing up with only one parent or none, losing a good friend, a relative or a significant other, or moving away from the parents' home.
Results on self-reported film responses have been published in (Speck et al., 2019).

Oxytocin reactivity

Preliminary analysis showed ECreact and CCreact to be unrelated to verbal IQ, AVLT and age, as assessed by Spearman rank-order correlation. To assess if there was an interaction effect between group, gender, and version of experiment (see methods), we ran a three-way (factorial) MANOVA with ECreact and CCreact, followed by post-hoc ANOVAs.

There was no statistically significant three-way interaction between group, gender, and test version. Also, no significant simple two-way interaction was found. The three-way analysis of variance yielded a significant main effect for test version. Post-hoc ANOVA revealed a significant effect of group for ECreact, but not for CCreact, such that the average ECreact was significantly higher in patients, compared to controls. A significant effect of test version was found for CCreact but not for ECreact, CCreact being significantly higher when the CC films were shown before the EC films (test version 2). See results in table 4 of (Speck et al., 2019).

In summary, there was no significant change of oxytocin levels during viewing of the control film, while the emotional film condition induced oxytocin level increases in patients and decreases in healthy controls. This effect was stronger in female subjects (see table 3 of (Speck et al., 2019)).

Results on oxytocin reactivity have been published in (Speck et al., 2019).

Baseline correlation

We conducted a Spearman rank-order correlation to assess the relationship of baseline oxytocin with ECreact and CCreact. There was a significant moderate negative correlation of baseline oxytocin levels and ECreact but not CCreact.

Results on baseline correlations have been published in (Speck et al., 2019).

Psychopathology correlations

To assess if there is a relationship between symptom severity measures and ECreact/CCreact we conducted a Spearman rank-order correlation test. There were no significant correlations of PANSS with ECreact ($p>0.05$). However, we found a moderate negative correlation of CCreact with PANSS' "general psychopathology" subscale. We found no significant correlation with PANSS' negative and positive symptom scales.

We did not find significant correlations of ECreact or CCreact with neuroleptic dose (chlorpromazine equivalents) or duration of illness, as assessed by Spearman rank-order correlation.

Results on psychopathology correlations have been published in (Speck et al., 2019).

Empathy

We observed significantly lower cognitive empathy scores in schizophrenia patients, as assessed by MET. Further differentiation showed significant deficits (compared to healthy subjects) in recognition of positive emotions. There were also deficits in recognition of negative emotions, although not reaching statistical significance.

Importantly, we found no significant differences in emotional empathy, as measured by the MET emotional empathy subscale. Accordingly, patients' self-ratings on the IRI revealed less competence in perspective-taking (as a measure of cognitive empathy). Fantasy and empathic concern were similar in both subject groups, but we found that schizophrenia patients were much more likely to report experiencing anxiety and discomfort when faced with distress of others (personal distress).

Results on empathy measures have been published in (Montag et al., 2020b).

Correlations of empathy and oxytocin

In patients, higher oxytocin reactivity was related to lower negative valence cognitive empathy scores, ergo recognizing negative emotions. This effect was not seen in the control group. Additionally, in healthy controls, higher oxytocin reactivity during both control and emotional film conditions were related to lower self-ratings in the IRI "fantasy" dimension. This relationship was not found in the patient group. No other correlations were found between oxytocin reactivity and MET or IRI scores. Oxytocin baseline levels were related to neither MET nor IRI. Controlling for verbal IQ, AVLT and age did not change the above-mentioned results. Introducing these three control variables did however reveal a further association in schizophrenia patients: higher oxytocin baseline values were related to lower MET positive valence cognitive empathy scores, ergo recognition of positive emotions.

Results on correlations of empathy and oxytocin levels have been published in (Montag et al., 2020b).

Attachment and childhood adversity

We found significant differences of self-reported childhood adversity between patients and healthy subjects. On average, patients were more likely to have experienced

sexual and emotional abuse, as well as emotional and physical neglect. Patients were also more likely to show signs of anxious attachment patterns, as assessed by PAM. See detailed results in table 1 of (Speck et al., 2019).
In both schizophrenia and healthy controls group baseline OXT and OXT reactivities had no association with PAM or CTQ measures. Gender-differentiated analyses also showed no association.
Results on attachment styles and childhood adversity have been published in (Speck et al., 2019).

2.4. Discussion

In this study investigating oxytocin level changes induced by an emotional video-protocol in schizophrenia, we found pronounced oxytocin secretion during the presentation of emotionally laden film scenes in patients with schizophrenia when compared to healthy controls. This effect was not seen in a non-emotional control condition. The effect was strongest in female patients. Additionally, baseline oxytocin levels were lower in female patients when compared to healthy females. We found no baseline difference between male patients and controls (Speck et al., 2019).
We also observed significantly lower cognitive empathy scores in schizophrenia patients, as assessed by MET. Importantly, we found no significant differences in emotional empathy, as measured by the MET emotional empathy subscale. Accordingly, patients' self-ratings on the IRI revealed less competence in perspective-taking (as a measure of cognitive empathy). Fantasy and empathic concern were similar in both subject groups, but we found that schizophrenia patients were much more likely to report experiencing anxiety and discomfort when faced with distress of others (personal distress). We also found a significant association of MET cognitive empathy scores with oxytocin reactivity in schizophrenia patients, but not controls (Montag et al., 2020b).
Differences in baseline oxytocin in our overall sample showed a trend towards lower levels in schizophrenia patients, although not reaching significance (Speck et al., 2019). Lower levels have been previously reported (Goldman et al., 2008; Jobst et al.,

2014; Aydın et al., 2018), but evidence is far from being conclusive, as many studies report increased or similar oxytocin levels (Rubin et al., 2010, 2014; Walss-Bass et al., 2013). Gender-specific level differences have not been reported consistently. In our sample, female patients had significantly lower oxytocin levels than their healthy counterparts (Speck et al., 2019). Rubin et al reported no significant gender-related oxytocin level differences in a schizophrenia sample of medicated (Rubin et al., 2014) and unmedicated (Rubin et al., 2013) patients. Ozsoy et al. found lower oxytocin levels in female patients with depression when compared to males (Ozsoy et al., 2009).

We found no correlation of antipsychotic dose with either oxytocin baseline levels or reactivity (Speck et al., 2019). There are reports of baseline oxytocin level changes induced by antipsychotic medication in animal studies (Uvnäs-Moberg et al., 1992; Kiss et al., 2010), and similar effects have been described in humans (Beckmann et al., 1985). Second-generation antipsychotics have been shown to have a dose-dependent influence on oxytocin levels in cerebrospinal fluid (CSF), while no interaction was found with first-generation antipsychotics (Sasayama et al., 2012). Regarding our reported gender differences, there is data suggesting estrogen to act as a mediator in oxytocin regulation (Gimpl and Fahrenholz, 2001). There is evidence of hypoestrogenism in female schizophrenia patients (Bergemann et al., 2005), regardless of antipsychotic type or menstrual cycle phase. Consequently, hypoestrogenism might have been associated with lower oxytocin levels, but unfortunately analysis of estrogen levels was out of the scope of our study. Menstrual cycle irregularities induced by antipsychotics (Murke et al., 2011) and subsequent estrogen level anomalies could also be argued, but current evidence does not describe cycle-dependent oxytocin fluctuations (Rubin et al., 2010, 2011). However, our data shows no significant correlation of antipsychotic dose and oxytocin baseline levels or reactivity (Speck et al., 2019). Our female sample size is rather small, though, and the study was not powered to assess effects of different antipsychotics or detect smaller effects of antipsychotics on oxytocin and cycle phase.

Further, we found heightened oxytocin reactivity, meaning elevated levels after viewing video scenes of attachment and consecutive loss, in schizophrenia patients, with most prominent level changes in female patients (Speck et al., 2019), which was not

observed during the control condition. To eliminate the possibility of this effect being due to lower baseline oxytocin in female patients, leading to a higher relative, but not absolute serum level change, we conducted a second analysis with baseline oxytocin as a covariate. Result were not affected.

Barraza and Zak (Barraza and Zak, 2009) were the first to use a film-protocol to induce oxytocin response in healthy persons. Although they did not report a significant change in oxytocin levels after showing a 2-minute long emotional scene (father talking about his terminally ill child), they found that showing a control video (same scene, but with audio replaced: father talking about a day at the zoo) significantly lowered oxytocin levels. Comparing responses in both scenes, oxytocin levels after watching the emotional video were 47% higher than after the control condition.

Conversely, Munro et al (Munro et al., 2013) reported different oxytocin responses in 15 healthy women during a film showing. They used a 30 minute edited version of “AI: Artificial intelligence” (Spielberg, 2001) and analyzed oxytocin levels before the film, during a bonding scene and during an abandonment scene. Although oxytocin levels seemed to have a slight tendency to rise during the bonding scene (not significant), the biggest changes occurred during the abandonment scene, in which oxytocin levels decreased significantly. The research suggests that oxytocin response is most significant when situations of social loss are shown, as compared to scenes of bonding, but other than expected as a stress-induced reaction, blood levels decreased.

Evidence of oxytocin system reaction following a social stimulus in schizophrenia is scarce. Keri et al. reported blunted oxytocin responses in schizophrenia patients in a trust-related task, compared to healthy controls (Keri et al., 2009). Our results in healthy women are in agreement with previous research, where oxytocin serum levels decreased when viewing an abandonment scene (Munro et al., 2013). Previous reports have also shown lower oxytocin levels in normal cycling women following induction of negative emotion imagery (Turner et al., 1999).

Munro et al found significant differences in oxytocin reaction depending on whether a bonding or an abandonment scene was shown. Our film protocols depict a bonding scene in the beginning, to introduce the relationship between characters to our subjects. This is then followed by a scene of death of one of the characters, which

could elicit similar emotional reactions as abandonment scenes, considering both portray a great personal loss. However, patients and controls showed divergent OXT responses during this part of the experiment. Though a speculative explanation, it is possible that personally salient aspects of our chosen films differed between schizophrenia and control groups, with patients focusing on attachment wishes, and controls on experienced loss. Patients more often reported feeling an unfulfilled desire for relationship or feelings of solitude at debriefing, stating that attachment figures like the ones shown in the films were what they `never had'. This might be due to schizophrenia symptomatology leading to social isolation, or higher occurrence of adverse childhood circumstances in schizophrenia patients. In contrast, being more likely to have experienced close relationships, healthy subjects might have resonated more strongly with the fear of abandonment and loss.

Pronounced oxytocin reactivity in our protocol might also have been partly due to oxytocin's role as a mediator of social approach. As negative symptoms include asociality and social isolation, promoting avoidance of interpersonal bonding (McCarthy et al., 2018), when faced with situations where social interaction and bonding is imminent (as well as when viewing movie scenes depicting interpersonal bonding) schizophrenia patients might exhibit a compensatory oxytocin release, to act as a buffer for facilitating social approach (Preckel et al., 2014).

Oxytocin levels are also sensitive to stress. In a model termed "tend and befriend", Taylor et al. (Taylor et al., 2010) suggest a role of oxytocin as a response hormone in the context of social stress, including social loss. Oxytocin then leads to increased sensitivity and affiliative motivation (Gimpl and Fahrenholz, 2001; Onaka, 2004; Bartz et al., 2011). Interestingly, this effect was found to be more pronounced in women (Taylor et al., 2000, 2010).

Pronounced personal distress in schizophrenia (Montag et al., 2007; Bonfils et al., 2017), confirmed in our patient sample, might be an additional modulator of oxytocin response, as oxytocin seems to act as a buffer, modulating anxiety and stress responses (Kirsch et al., 2005; Olff et al., 2013; Neumann and Slattery, 2016).

According to the "tend and befriend" model, our observed elevated oxytocin level changes in schizophrenia patients might have been secondary to pronounced levels

of emotional distress following viewing of empathy-inducing films. Both attachment and loss can be interpreted as social stressors (Stuke et al., 2020). As perception of social threat might elevate oxytocin levels (De Dreu and Kret, 2016), increased levels in our schizophrenia group might also be partly due to increased vigilance to social threat, as well as bonding-induced stress (Stuke et al., 2020) in patients.

Current evidence suggests that oxytocin has inhibitory effects in the amygdala (Domes et al., 2007a), dampening both physiological (Norman et al., 2011) and subjective (Heinrichs et al., 2003) responses to stress. Higher levels have been shown in individuals suffering from severe social anxiety (Hoge et al., 2008). Additionally, pronounced attachment anxiety seems to correlate with higher oxytocin levels (Marazziti et al., 2006). Consistent with our results, there is evidence of pronounced oxytocin system sensitivity to social stressors in women (Barraza and Zak, 2009; Taylor et al., 2010). In contrast, self-reported ratings of personal relevance of shown film scenes and arousal during viewing did not correlate to oxytocin levels or reactivity in our schizophrenia sample. There is however evidence of a possible discrepancy between autonomous arousal and experiential aspects of emotion in schizophrenia (Kring and Neale, 1996). Evidence on oxytocin effects on the amygdala are not conclusive, though, as it may even increase amygdala activity in women following negative emotional stimuli (Domes et al., 2010; Lischke et al., 2012).

Our second publication focused on associations of oxytocin and different measures of empathy in schizophrenia as its main subject (Montag et al., 2020b). Consistent with results from previous research, our data suggests significant deficits of cognitive empathy in schizophrenia but preserved self-rated emotional empathy, as assessed by MET, replicating results of Lehmann et al. (Lehmann et al., 2014). Self-ratings on the IRI suggest, however, that our patients were more prone to feeling emotional distress when faced with others in need, when compared to healthy controls.

Lower MET cognitive empathy scores and IRI “fantasy and “perspective taking” self-ratings were associated with lower verbal IQ, AVLT and age. This was to be expected, since purely cognitive aspects of social cognition are dependent on general cognition (Brüne, 2005).

Our data shows a significant association of cognitive empathy as assessed by MET cognitive empathy scores with oxytocin reactivity in the schizophrenia group, such that patients with more pronounced oxytocin level increases after viewing emotional film scenes had a higher probability of misidentifying negative emotions. This effect was not present in healthy controls. Analogous to our analysis of oxytocin reactivity, we conducted a second analysis using baseline oxytocin as a control variable. The above-mentioned correlation using this method was even more pronounced. Additionally, we found a significant negative correlation between baseline oxytocin levels and positive valences of cognitive empathy, as assessed by MET, in patients (Montag et al., 2020b). Results above suggest that misinterpretation of negative emotions in our movie scenes might have been a factor contributing to differences in measured oxytocin reactivity between patients and healthy controls. While correlated, the exact mechanisms by which oxytocin and cognitive empathy are related remain unclear. It is possible that, in schizophrenia, deficits in cognitive empathy lead to misinterpretation of social situations, causing interpersonal distress, which is then potentiated by dysfunctional emotion regulation strategies, and might lead to oxytocin system hyperresponsiveness – as there is evidence of increased oxytocin system reactivity in emotional and attachment-related vulnerability (Kéri and Kiss, 2011; Tabak et al., 2011; Crespi, 2016).

However, as the oxytocin system is related to multiple emotional processes, its dysfunction in schizophrenia is most likely multifactorial. For instance, early life experiences are an important factor in regulation of oxytocin effects (Feldman, 2017) and childhood trauma has been associated with lower oxytocin levels (Heim et al., 2009; Opacka-Juffry and Mohiyeddini, 2012). Evidence from individuals with experiences of childhood sexual abuse suggest increased (Seltzer et al., 2014) or decreased (Pierrehumbert et al., 2010) stress-induced oxytocin levels. Schizophrenia patients are more likely to have had traumatic childhood experiences than healthy controls (Read et al., 2005), and frequently present insecure attachment styles (Harder, 2014). This was confirmed in our patient group by CTQ and PAM, but we found no association between either parameter and baseline oxytocin or oxytocin reactivity. However, this question was not our focus and our study was most likely

underpowered to answer it. Oxytocin responses in schizophrenia might thus not only be disease-mediated, but at least partially be due to adverse early life experiences.

Limitations, clinical relevance and further research questions

As most emotional effects of oxytocin presumably take place in the central nervous system, oxytocin levels in the cerebrospinal fluid (CSF) (as a surrogate for measuring its release in the brain through intracerebral microdialysis) could be a more precise measure of its behavioral effects. Unfortunately, the invasive nature of CSF collection in humans also makes research with this fluid difficult. Thus, most research in clinical settings focuses on peripheral oxytocin levels, measured directly in the serum or indirectly in saliva samples. There is some evidence of coordinated release of oxytocin in CSF and peripheral blood (Neumann and Landgraf, 2012). Triggered by many physiological stimuli, such as birth, sexual activity, and various forms of stress, oxytocin release seems to be coordinated in both fluids, its effects being synergistic (Engelmann et al., 2004; Neumann, 2007).

A significant limitation to all studies involving either the peripheral measurement or the intranasal application of oxytocin is the short half-life of oxytocin. When given intravenously, synthetic oxytocin has an elimination half-life of 3-4 minutes (Christensen et al., 2014) (although after intranasal application elevated saliva levels could be measured up to 2 hours after (Huffmeijer et al., 2012) - importantly, this is not the same as elimination half-life). This poses a problem for all studies involving oxytocin, since the time frame to collect samples or to conduct psychometric testing is small. Clearance patterns for endogenous oxytocin remain unknown. Moreover, the time-dependent nature of oxytocin release after emotional stimuli is yet unknown, but it could be brief and pulsatile, as it is during lactation (Armstrong and Hatton, 2006). One study partially addressed some of these concerns by measuring oxytocin saliva levels in 10-minute intervals (Engert et al., 2016). Similar protocols measuring plasma levels in even briefer intervals after a stimulus are needed.

We took blood samples within a defined time frame and chilled samples immediately after extraction, to inhibit any protease action. Some studies added protease inhibitors to blood samples, but, as Christensen et al. (2014) noted, this may not be necessary,

as research suggests that oxytocin is stable for up to 17 hours in blood plasma at room temperature (Zhang et al., 2011). Nevertheless, we suggest future studies to collect various blood samples in rapid succession, to determine if there are in fact oxytocin peaks and how blood levels behave within a certain time frame after stimuli.

Our study is also limited by its sample size, as it is underpowered to detect more subtle oxytocin level changes and correlations. It does however serve as a hypothesis-generating study. We designed and utilized a novel study protocol and demonstrated its usefulness in schizophrenia patients. Our reported baseline oxytocin levels on both schizophrenia patients and healthy controls represent important data for planning and interpretation of further studies using similar paradigms, e.g. effect sizes as a basis for calculating sample sizes.

As we discussed, stress-related responses might have played a role in our observed oxytocin level changes. Unfortunately, we did not collect physiologic parameters such as blood pressure, heart rate or serum levels of cortisol and biogenic monoamines. Neither did we collect serum levels of sex hormones such as estrogen, which limits interpretation of our observed results in female participants. Further, we only conducted one behavioral empathy test, the MET, and one test of self-reported empathy, the IRI. However, both have been demonstrated to be useful in schizophrenia samples (Lehmann et al., 2014; Montag et al., 2020a).

Our study shows that oxytocin reactivity differs significantly between male and female patients, prompting further gender-differentiated research. Gender-specific oxytocin effects have been neglected in research regarding oxytocin as a therapeutic agent. For example, recent metanalyses of oxytocin's role as a therapeutic agent in schizophrenia have shown that eligible trials included mainly male participants: between 70 and 100%, with a mean value of 81%.

As attachment, vulnerability to psychiatric disorders, social experiences, social behavior, responses to stress and oxytocin response are all sexually dimorphic (Carter, 2017), we suggest further research not only focus on female patients, but consider that oxytocin dysfunction in schizophrenia is a multifactorial phenomenon, and identifying patient subgroups based on these factors might bring different therapy results. Also, recent metanalyses have focused on oxytocin effects on schizophrenia symptoms, not

on functional impairment. There is evidence of oxytocin effects on social and non-social cognition, but results are contradictory (Bradley and Woolley, 2017). Moreover, its effects on specific functional outcomes related to interpersonal behavior, like autistic withdrawal, or in turn, the ability to interact, to approach others, to communicate, and eventually to form and to maintain interpersonal relationships have, to our knowledge, not been studied in this condition.

Although not a focus in this study, oxytocin is closely related to a similar peptide, vasopressin, which closely interacts with the oxytocinergic system modulating social response. Evidence suggests it complements and modulates oxytocin effects (as well as being modulated by oxytocin itself). Some authors suggest oxytocin may be related to more passive aspects of attachment, while vasopressin may activate more aggressive and possessive attachment behavior (Carter, 2017). Further studies might consider vasopressin as well as oxytocin pathways in the context of schizophrenia and social functioning.

Oxytocin effects are still not well understood. For instance, additionally to its stress relieving effects, it also shows anxiogenic effects (Peters et al., 2014). It is still unclear under which conditions oxytocin produces which effects, and more studies are required to better understand its therapeutic use.

Among other findings, our study is the first to show that in schizophrenia, particularly in women, there is pronounced oxytocin reactivity to a film stimulus, its levels increasing while showing emotional scenes of social loss. This response was not seen in healthy controls. As a strength of our study, it can be mentioned that the radioimmunoassay method with sample extraction was used, making high quality measurements possible. Few studies involving schizophrenia samples have used this method (Strauss et al., 2015a; Busnelli et al., 2016).

Furthermore, we present a novel model of measuring oxytocin reactivity and discuss its advantages and limitations. As discussed, psychometric tests designed to measure peripheral oxytocin would greatly profit from further research on the kinetics of endogenous oxytocin. Finally, further studies are needed on the role of the oxytocinergic system as a contributor to psychotic vulnerability and psychosocial dysfunction.

2.5. Summary of results

In our schizophrenia sample, particularly in women, there was pronounced oxytocin reactivity to a film stimulus, its levels increasing while showing emotional scenes of social loss. This response was not seen in healthy controls. Additionally, cognitive empathy was inversely related to both baseline oxytocin levels and oxytocin reactivity in schizophrenia patients. Our results suggest that regulatory systems involving endogenous oxytocin might be affected in schizophrenia. This justifies further research in the field of endogenous oxytocin responses to social and empathy-related stimuli in schizophrenia.

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3. Eidesstattliche Versicherung

„Ich, Lucas Guilherme Speck, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Endogenes Oxytocin bei Patient*innen mit Schizophrenie - Veränderungen der Plasma-Oxytocinkonzentration in Reaktion auf emotionale Filmstimuli und Zusammenhänge mit dem empathischen Erleben im Vergleich zu Gesunden“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.
Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.
Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.
Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.
Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

4. Ausführliche Anteilserklärung

Ausführliche Anteilserklärung an der erfolgten Publikation als Top-Journal im Rahmen der Promotionsverfahren zum Dr. med.

Publikation: Lucas G Speck, Johanna Schöner, Felix Bermpohl, Andreas Heinz, Jürgen Gallinat, Tomislav Majić, Christiane Montag, Endogenous oxytocin response to film scenes of attachment and loss is pronounced in schizophrenia, Social Cognitive and Affective Neuroscience, Volume 14, Issue 1, January 2019, Pages 109–117

Herr Lucas Guilherme Speck, geboren in Freiburg i.B., hatte folgenden Anteil:

Thema:
Der Promovend hatte maßgeblichen Einfluss auf die Fragestellungen der Promotion. Ausgangspunkt war das Thema Empathie und oxytocinerges System bei Patient*innen mit Schizophrenie. Hieraus wurden folgende Fragestellungen herausgearbeitet:

(1) Beziehungen zwischen Empathie und Oxytocin bei Schizophrenie: Hierfür wurde die Reaktion des oxytocinergen Systems auf einen emotionalen Stimulus untersucht. Dieses Protokoll wurde gemeinsam von Frau PD Dr. Christiane Montag und Herrn Speck entwickelt. Basierend auf publizierten Arbeiten zur Reaktivität des Oxytocin-Systems wurde von Herrn Speck ein Video-basiertes Protokoll mit Kinderfilmen vorgeschlagen.

(2) Altruismus und Vertrauen bei Schizophrenie: Empathie und prosoziales Verhalten sind eng miteinander verknüpft. Zur Untersuchung dieser Fragestellung wurden zwei Verhaltensexperimente, das „Trust Game“ und eine veränderte Version des „Dictator Game“, für die Zwecke der Studie adaptiert und durchgeführt. Basierend auf einem Geldspiel zwischen Probanden und einer fiktiven Person wurde prosoziales Verhalten untersucht. Die Fragestellung wurde durch Herrn Speck vorgeschlagen, mögliche Studiendesigns wurden von ihm herausgearbeitet. Die Auswahl der Verhaltensexperimente erfolgte durch den Promovenden. Diese Studienergebnisse

wurden noch nicht veröffentlicht.

(3) Der Antrag zur Studienzulassung durch die Ethikkommission wurde von Herrn Speck verfasst, Beratung und Korrekturen erfolgten durch Frau PD Dr. Montag.

Methodik und Ergebnisse:

(1) Das gesamte Studienprotokoll wurde von Herrn Speck in enger Zusammenarbeit mit Frau PD Dr. Montag entwickelt. Notwendige Übersetzungen (z.B. Psychosis Attachment Measure) wurden von Herrn Speck initiiert bzw. durchgeführt.

(2) Probanden wurden sowohl von Herrn Speck als auch von Frau Johanna Schöner (Coautorin) und Frau PD Dr. Montag rekrutiert. Die Rekrutierung, Aufklärung und Durchführung der Experimente erfolgten bei ca. 50% der Probanden durch Herrn Speck.

(3) Die Statistische Aufarbeitung und Auswertung sowie Interpretation der Studienergebnisse für die oben genannte Publikation erfolgte nach Beratung und Rücksprache mit der Betreuerin maßgeblich durch Herrn Speck. Aus dieser statistischen Auswertung entstanden Tabellen 1, 2, 3 und 4 der oben genannten Publikation. Die Tabellen wurden von Herrn Speck selbstständig zusammengestellt.

Verfassung der Publikation:

(1) Das Manuskript zur Publikation wurde (mit Hilfe von Beratung, Korrekturen und Ergänzungen durch die Betreuerin und Coautoren) von Herrn Speck selbstständig verfasst. Strukturelle Gliederung und inhaltliche Formulierungen erfolgten durch Herrn Speck als federführender Autor in Absprache mit den Coautoren. Notwendige Revisionen nach Einreichung des Papers wurden ebenfalls zu größtem Teil von Herrn Speck übernommen.

(2) Die Literaturrecherche wurde bis auf die Auswahl weniger Referenzen (nach Vorschlag der Betreuerin) durch Herrn Speck selbständig durchgeführt.

(3) Herr Speck hatte einen Hauptanteil and der kritischen Würdigung der Ergebnisse sowie an der Identifikation der relevanten Aussagen und Limitationen der Studie.

(4) Diese Dissertation (einschließlich Abstracts und Manteltext) wurde von Herrn Speck selbstständig nach begleitender Beratung durch Frau PD Dr. Montag verfasst.

_____
Unterschrift, Datum und Stempel der erstbetreuenden Hochschullehrerin

_____
Unterschrift des Doktoranden/der Doktorandin

5. Auszug aus der Journal Summary List

Journal Data Filtered By: **Selected JCR Year: 2017** Selected Editions: SCIE,SSCI Selected Categories: **"PSYCHOLOGY"** Selected Category Scheme: WoS **Gesamtanzahl: 78 Journale**

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	Annual Review of Psychology	18,461	22.774	0.022550
2	Annual Review of Clinical Psychology	4,926	13.278	0.010550
3	PSYCHOLOGICAL BULLETIN	47,657	13.250	0.025950
4	PSYCHOTHERAPY AND PSYCHOSOMATICS	3,597	13.122	0.005520
5	PSYCHOLOGICAL REVIEW	27,474	7.230	0.009110
6	JOURNAL OF CHILD PSYCHOLOGY AND PSYCHIATRY	18,604	6.486	0.023410
7	PSYCHOLOGICAL MEDICINE	23,080	5.475	0.039400
8	DEPRESSION AND ANXIETY	7,923	5.043	0.015870
9	INTERNATIONAL JOURNAL OF EATING DISORDERS	8,732	3.897	0.010160
10	PSYCHOSOMATIC MEDICINE	12,288	3.810	0.010150
11	Journal of Neuropsychology	582	3.786	0.001340
12	**Social Cognitive and Affective Neuroscience**	**6,443**	**3.500**	**0.020770**
13	PSYCHO-ONCOLOGY	10,201	3.455	0.019830
14	NEUROBIOLOGY OF LEARNING AND MEMORY	6,610	3.244	0.012470

6. Druckexemplar der ausgewählten Publikation

OXFORD

Social Cognitive and Affective Neuroscience, 2019, 109–117

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Original article

Endogenous oxytocin response to film scenes of attachment and loss is pronounced in schizophrenia

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Abstract

Background: Oxytocin (OXT) is critically involved in the regulation of attachment and interpersonal function. In this study, emotional children's movies were used to stimulate OXT secretion in patients with schizophrenia and healthy controls (HCs). Furthermore, associations of OXT levels with measures of attachment style (Psychosis Attachment Measure), childhood adversity (Childhood Trauma Questionnaire) and symptom severity [Positive and Negative Syndrome Scale (PANSS)] were considered. **Methods:** In 35 patients with schizophrenia and 35 matched HCs, radioimmunoassay with sample extraction was used to determine OXT plasma levels before and after viewing of movie scenes portraying emotional bonding and loss and compared to a non-emotional condition. **Results:** Statistical analysis indicated lower baseline OXT levels in female patients than in all other groups. OXT reactivity during emotional movies was significantly higher in patients when compared to HCs. OXT reactivity during the control movie related to PANSS 'general psychopathology'. No significant associations appeared between baseline or induced OXT levels and other PANSS subscales, attachment style or childhood adversity in patients. **Conclusions:** Our findings suggest differences of baseline OXT and a higher OXT reactivity toward strong emotional stimuli in patients with schizophrenia, suggesting a role of OXT as a gender- and context-dependent modulator of socio-emotional function.

Key words: schizophrenia; oxytocin; emotion induction; attachment; trauma

Introduction

In recent decades, disturbances of empathy and emotional responsivity have gathered increasing attention in schizophrenia research. A reduced capacity to emotionally resonate with others, to understand and to regulate other induced feelings and relationship distress might complicate the formation of intimate bonds. In addition, individuals suffering from psychotic disorders are often burdened with substantial childhood adversity and may lack stable attachment experiences (Berry *et al.*, 2008). The spectrum of attachment-related dysfunctions, including conditions like autism, borderline personality disorder or schizophrenia, has been consistently linked to the oxytocinergic system. Oxytocin (OXT), a neurohypophyseal hormone and neurotransmitter, is considered to be an important modulator of social cognition and empathy (Domes *et al.*, 2007; Bartz *et al.*, 2011). Its prosocial effects have consistently been reported from studies investigating mother–infant (Feldman *et al.*, 2007) and pair bonding (Young and Wang, 2004), attachment (Buchheim *et al.*, 2009), cooperation (De Dreu and Kret, 2016) and trust

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(Kéri and Kiss, 2011). De Dreu and Kret (2016) speak of an OXT-biased, biobehavioral approach–avoidance principle, with OXT acting on social salience and reward, as well as dampening vegetative responses to social threats and stressors. Furthermore, OXT may facilitate affiliation by promoting in-group empathy, cooperation and trust, but also serve the protection from out-group danger by up-regulating vigilance and defense-motivated aggression. Therefore, OXT might affect more than one of the functional systems implicated in psychotic vulnerability by modulating attachment, social approach, interaction experience and mentalizing capacity on the one hand and the perception of aberrant salience and social threat on the other (Olff *et al*., 2013; Debbané *et al*., 2016). Early suggestions of OXT as a 'natural antipsychotic' and evidence from animal studies demonstrating OXT to counteract excessive mesolimbic dopamine and cortical hypoglutamatergia led to the assumption that OXT signaling might be altered in schizophrenia (Macdonald and Feifel, 2012). However, results from trials using intranasal OXT in patients with schizophrenia have been mixed, some reporting improvement of positive and negative symptoms or improvement of specific deficits, while others reported no benefit (Feifel *et al*., 2016; Bradley and Woolley, 2017). Accordingly, the role of endogenous OXT remains inconclusive, with studies reporting lower (Goldman *et al*., 2008; Jobst *et al*., 2014; Aydin *et al*., 2018) or higher (Legros *et al*., 1992; Strauss *et al*., 2015) cerebrospinal fluid (CSF) and plasma OXT levels in patients with schizophrenia, as well as varying associations with symptom load (Goldman *et al*., 2008; Kéri *et al*., 2009; Rubin *et al*., 2010; Jobst *et al*., 2014). A small number of studies report associations of plasma OXT levels with social cognitive capacity in schizophrenia patients (Goldman *et al*., 2008; Walss-Bass *et al*., 2013; Strauss *et al*., 2015), the avoidance of angry faces (Brown *et al*., 2014) or the perception of faces as happier (Rubin *et al*., 2011). OXT measurements in the absence of a social stimulus seem highly variable, and therefore stimulus-evoked OXT level changes were considered to be more reliable (Zak *et al*., 2005; Kéri and Kiss, 2011). In a single study, Kéri and coworkers showed OXT responses toward trust-related interactions to be blunted in schizophrenia patients (Kéri *et al*., 2009).

The goal of this study was to compare baseline endogenous OXT levels as well as OXT level changes induced by social stimuli between groups of schizophrenia patients and healthy controls (HCs). To activate the endogenous OXT system, pivotal emotional scenes from children's movies like 'Bambi' were shown to the participants. All selected scenes presented situations of bonding and loss of an attachment figure. The main hypotheses were that schizophrenia patients would (i) differ in OXT baseline levels when compared to HCs and (ii) show reduced OXT reactivity in the emotional, but not in a non-emotional control condition. On an exploratory basis, it was hypothesized that baseline and induced OXT levels in patients would be associated with (i) symptom severity, (ii) history of childhood trauma and (iii) attachment style, which have been linked with OXT dysfunction in previous studies (Heim *et al*., 2009; Rilling, 2009).

Materials and methods

Participants

The study was approved by the local ethics committee; subjects gave written informed consent. Thirty-five in- and outpatients with paranoid schizophrenia (PS; 23 males), aged 18–65, were recruited from Charité Universitätsmedizin Berlin, Psychiatric University Clinic at St. Hedwig Hospital. Diagnosis and symptom severity were confirmed by the treating psychiatrist using structured clinical interviews for DSM-IV and the Positive and Negative Syndrome Scale (PANSS). All patients were stabilized, showing at best mild to moderate symptom load. PS showing antisocial personality traits were excluded (SCID I; SCID II items for antisocial personality disorder, German versions). Thirty-five HC subjects (HC; 23 males), matched for age and verbal IQ, were recruited by printed and direct verbal advertisement in the hospital and university (cleaning and nursing staff, students) and screened with structured interviews (SCID II, MINI; Table 1). Exclusion criteria for both groups were DSM-IV axis-I or axis-II disorders (except schizophrenia for patients), hormonal contraception, pregnancy and lactation. HC reporting axis-I mental disorders in their first- or second-degree relatives were excluded. Of note, none of the participants manifested postraumatic symptoms or PTSD. Participants had to abstain from alcohol/drug consumption 24 h prior to testing. Menstrual cycle phase of female subjects was based on the timeframe of their last menses. Coded as menses/follicular/luteal/menopause/unknown, distribution was n = 2/2/5/1/2 in the PS group, and n = 0/2/3/2/5 in HC women (χ^2 = 4.119, P = 0.390).

Neurocognition

A multiple choice vocabulary test (Mehrfach-wahl-wortschatztest, MWT-B) was applied to estimate verbal intelligence. Additionally, a German version of the Auditory Verbal Learning Test (AVLT) was used as a measure of general cognitive functions such as multiple verbal memory components and executive functions. Means of the first five presentations (AVLT$^{(1-5)}$) were used for analysis.

Childhood adversity and attachment style

The 28-item form of the Childhood Trauma Questionnaire (CTQ-SF; Bernstein *et al*., 2003) was used to assess adverse childhood experiences. This retrospective self-report measure assesses five types of maltreatment in separate subscales—emotional abuse, sexual abuse, physical abuse, emotional neglect and physical neglect. Each subscale includes five items that are rated on five-point Likert scales. Psychometric properties of the original five-factor solution were confirmed for the German translation (Dudeck *et al*., 2015) and its usefulness was demonstrated in schizophrenia patients (Kim *et al*., 2013). An authorized German translation of the 16-item Psychosis Attachment Measure (PAM; Berry *et al*., 2008) estimated two aspects of insecure attachment, anxiety and avoidance (eight items each), by self-report, on a four-point Likert scale. Psychometric properties and factor structure of the English version are reported from a psychosis sample (Berry *et al*., 2008).

Video-stimulated OXT reactivity

For the induction of attachment-related feelings (emotion induction condition: EMOI), scenes from three children's movies were chosen, giving an introduction to the relationship in question (bonding) and ending with the death of the attachment figure (loss, empathy with the main character). We chose the films 'Bambi' (6 min, 37 s), 'The Lion King' (5 min, 44 s) and 'UP!' (4 min, 21 s), portraying the loss of a mother, a father and a beloved wife, respectively. To obtain a reliable and strong emotion induction effect, all videos were presented consecutively in the same order and confronted participants with the same basic need of bonding and belonging, while romantic

Table 1. Demographic data and disease characteristics for schizophrenia patients and HCs

	HC	Schizophrenia	Statistics
Number of participants	35	35	
Gender (m/f)	23/12	23/12	[1]$\chi 2 = 0.000$
Age	36.0 ± 10.4	40.4 ± 8.8	[2]T = 1.882
Verbal IQ	114.1 ± 17.6	107.2 ± 18.0	[3]U = 471.000
AVLT(1–5) score	10.7 ± 2.0	8.5 ± 2.2	[2]T = −4.340***
Educational years	14.2 ± 2.5	11.9 ± 2.4	[3]U = 140.000**
CTQ			
physical abuse	6.5 ± 3.6	7.2 ± 3.2	[3]U = 353.000
sexual abuse	5.2 ± 0.9	7.4 ± 4.4	[3]U = 295.000***
emotional abuse	7.7 ± 3.6	10.7 ± 4.1	[3]U = 238.000***
emotional neglect	9.5 ± 3.9	12.0 ± 4.6	[3]U = 318.000*
physical neglect	6.8 ± 2.3	8.7 ± 4.1	[3]U = 286.000**
PAM			
anxiety	2.1 ± 0.7	2.5 ± 0.5	[3]U = 278.000***
avoidance	2.0 ± 0.5	2.0 ± 0.4	[3]U = 507.500
Age at first manifestation	-	27.7 ± 8.9	-
Duration of illness	-	12.4 ± 8.4	-
Antipsychotic dose (CPZ, [mg])			
Total	-	386.4 ± 349.7	-
FGA	-	64.2 ± 148.6	-
SGA	-	304.2 ± 322.0	-
PANSS			
positive score[4]	-	18.2 ± 9.8	-
negative score[4]	-	19.7 ± 7.5	-
general psychopathology[4]	-	32.6 ± 11.0	-

[1]: $\chi 2$-Test; [2]: T-Test for independent samples; [3]: Mann–Whitney-U Test. *: $P < 0{,}05$; **: $P < 0{,}01$; ***: $P < 0.001$. Significant results are indicated in bold type. [4]: $N = 32$. AVLT: Auditory Verbal Learning Test; CPZ: Chlorpromazine equivalent; CTQ: Childhood Trauma Questionnaire; FGA: first generation antipsychotics; PAM: Psychosis Attachment Measure; PANSS: Positive and Negative Syndrome Scale; SGA: second generation antipsychotics.

attachment played a minor role. A scene from a weather documentary represented the control condition (CON; 3 min, 37 s). The CON phase was shorter than the EMOI phase to prevent the induction of negative emotions like boredom. EMOI and CON films were balanced regarding their order of appearance (test version 1: EMOI first; test version 2: CON first). All subjects were tested between 10 a.m. and 1 p.m. to rule out natural fluctuations of OXT levels. Subjects were given a 60 min break between conditions.

After each movie scene, three questions were presented to the subject: (i) 'How strongly did you feel with the main character?' (EMPATHY), (ii) 'How much have you felt stressed or fearful?' (AROUSAL) and (iii) 'How relevant is this scene to your life?' (RELEVANCE). Subjects were asked to answer on a scale of 1 to 6. In the CON condition, the first question was replaced with (i) 'How relaxed were you during the film?' (RELAXATION), since the documentary did not feature any empathy-inducing character.

At debriefing after EMOI, participants were asked whether they would share their thoughts and feelings during the films with the experimenter. This was rated on a six-point scale ranging from 'not at all' to 'completely' (TRUST). Participants were then asked to take a short note of what they had felt.

A peripheral venous catheter was placed 30 min prior to testing. Before the first EMOI film and 1 min after the last EMOI film, as well as before and 1 min after the CON condition, citrated plasma samples were taken, centrifuged immediately and frozen (−28°C). The timing of plasma sampling was based on protocols using video-based stimulation or trust-related interventions (Barraza and Zak, 2009; Kéri *et al.*, 2009; Munro *et al.*, 2013).

OXT concentrations were determined by radioimmunoassay (RIA) using solid phase sample extraction by Prof. Dr Rainer Landgraf, RIAgnosis, Munich (http://www.riagnosis.com). Assay sensitivity for this method is in the 0.1 pg/ml sample range, intra- and inter-assay variability is under 10% and no significant cross-reactivity is reported. Details of extraction method, analysis and validation are reported elsewhere (http://www.riagnosis.com; Neumann *et al.*, 2013).

Statistical analysis

Normal distribution was determined by Kolmogorov–Smirnov tests. OXT reactivity was calculated according the following equation:

$$EMOI\ reactivity = \frac{[Oxytocin]\ after\ EMOI\ films}{[Oxytocin]\ before\ EMOI\ films}$$

$$CON\ reactivity = \frac{[Oxytocin]\ after\ control\ film}{[Oxytocin]\ before\ control\ film}.$$

OXT reactivities were log-transformed to attain normal distribution [reactEMOI = log(EMOI reactivity); reactCON = log(CON reactivity].

Results

Socio-demographic data, illness characteristics, CTQ-SF and PAM scores are shown in Table 1. PANSS measures for three patients were not available. Patients scored significantly lower than healthy subjects in AVLT(1–5) values and educational years but indicated significantly more adverse childhood experiences

Table 2. Self-ratings of emotional empathy, arousal or relaxation experienced during EMOI (sum) and CON, as well as personal relevance of stimuli, and willingness to trustfully share thoughts and feelings related to EMOI (TRUST), by patients with schizophrenia and HCs

	HCs	Schizophrenia	Statistical tests
EMOI films			
EMPATHY	13.63 ± 2.64	12.26 ± 3.50	U = 474.500
AROUSAL	6.14 ± 3.42	5.80 ± 2.49	U = 612.000
RELEVANCE	9.63 ± 4.09	8.63 ± 3.29	U = 536.500
TRUST	5.18 ± 1.19	4.56 ± 1.54	U = 392.500*
CON film			
RELAXATION	4.80 ± 1.05	4.07 ± 1.41	U = 428.500*
AROUSAL	1.20 ± 0.47	1.67 ± 1.13	U = 479.500*
RELEVANCE	2.48 ± 1.46	2.51 ± 1.65	U = 529.000

N = 35/35, means, s.d.; Mann–Whitney U test: ∗: $P < 0.05$; Significant results are indicated in bold type. EMOI: presentation of emotional films, CON: presentation of control film.

on all CTQ-SF subscales apart from physical abuse, and more attachment anxiety on the PAM than controls.

Behavioral data

PS showed significantly lower self-rated RELAXATION and higher AROUSAL values during the CON film than HC. No group differences appeared for EMPATHY, AROUSAL or subjective RELEVANCE related to the EMOI condition, but PS were slightly less willing to share their thoughts and feelings with the experimenter (TRUST; Table 2). No significant associations were detected between TRUST and PANSS total or subscores (all $P > 0.05$). Qualitative debriefing information was available from $n = 31$ PS and $n = 28$ HC. Topics differed between groups, while the emotional focus was reflected by the majority of participants in both groups (PS/HC: refused answer: 1/0; rational account: 4/1; emotional but impersonal account: 2/7; emotional personal recollection: 5/10; fear of loss and/or longing for attachment: 14/10; loneliness: 5/0).

Baseline OXT

Baseline OXT levels did not differ significantly between patients and HCs. Group comparisons of the male and female subsamples yielded no differences in males but showed significantly lower OXT levels in female patients compared to female controls (Table 3). Analysis of covariance (ANCOVA) was performed with log-transformed baseline OXT levels as the dependent variable, group and gender as factors and age as a covariate. There was a significant interaction between group and gender, $F(1,70) = 5.663$; $P = 0.02$, where female PS had lower baseline OXT levels than all other groups. There were no significant main effects of diagnosis, gender or age.

OXT reactivity

PS showed significantly higher OXT levels after emotion/empathy induction (EMOI) than before (Wilcoxon test, $Z = -2{,}129$, $P = 0.033$), but in HC there were no differences before and after both conditions (EMOI: $Z = -1{,}368$, $P = 0.171$; CON: $Z = -0{,}655$, $P = 0.512$). Accordingly, PS showed a significantly higher OXT reactivity during emotion/empathy induction (EMOI) compared to HC (Table 3). To assess interaction effects between diagnostic group, gender and sequence of the experiments (version 1 *vs* version 2), a factorial multivariate analysis of variance (MANOVA) with logarithmized OXT reactivities (reactEMOI, reactCON) as dependent variables, and group, gender and test version as independent factors, followed by *post hoc* ANOVAs was run. Homogeneity of variances was confirmed by Box-M and Levene's tests ($P > 0.05$). Partial eta^2 ($_p\eta^2$) was used as an estimate of effect sizes. Significant main effects were found for group and test version (Table 4). *Post hoc* ANOVA revealed a significant effect of diagnostic group for reactEMOI, but not for reactCON, reactEMOI being significantly higher in PS, compared to HC. A significant effect of test version was found for the CON condition, but not for EMOI. ReactCON was significantly higher when CON was shown first. There were neither statistically significant interactions between group and gender or test version, nor between gender and test version, and no significant main effect of gender was found (Table 4).

Of note, the effect of diagnostic group on reactEMOI was not altered by inclusion of baseline OXT levels as a covariate ($F[2,61] = 3.381$, $P = 0.041$, $_p\eta^2 = 0.10$; *post hoc*: $F[1,62] = 6.386$, $P = 0.014$, $_p\eta^2 = 0.14$).

Table 3. Baseline OXT levels and reactivity of endogenous OXT (ratio OXT after/before film presentation) in schizophrenia patients and HCs

	HC	Schizophrenia	Statistics
OXT at baseline [pg/ml]	5.48 ± 4.50	4.59 ± 3.35	U = 576.000
Males	4.64 ± 3.84	5.38 ± 3.87	U = 218.000
Females	7.10 ± 5.36	3.07 ± 0.96	U = 31.000*
OXT EMOI reactivity	0.96 ± 0.38	1.22 ± 0.50	U = 371.000*
Males	1.01 ± 0.39	1.15 ± 0.42	U = 190.000
Females	0.85 ± 0.34	1.36 ± 0.64	U = 29.000*
OXT CON reactivity	1.07 ± 0.55	1.18 ± 0.48	U = 509.000
Males	1.08 ± 0.62	1.13 ± 0.49	U = 225.000
Females	1.04 ± 0.39	1.27 ± 0.47	U = 58.000

N = 35/35, means, s.d.; Mann–Whitney U test: ∗: $P < 0.05$; Significant results are indicated in bold type. EMOI: presentation of emotional films, CON: presentation of control film.

Correlation analyses

On an exploratory basis, Spearman rank-order correlation coefficients served to assess the relationship between baseline OXT levels, OXT reactivities and socio-demographic and illness characteristics as well as measures of early adversity and attachment style.

Significant associations of baseline OXT, and OXT changes to EMOI or CON scenes with age, verbal IQ, AVLT[(1–5)] scores or educational years could not be determined. There were no significant correlations of baseline OXT, EMOI or CON reactivity with any of the film behavioral questions (all $P > 0.05$).

A moderate negative correlation of baseline OXT and EMOI reactivity, but not CON reactivity, appeared in the PS group ($r_s = -0.417$, $P = 0.013$), but did not reach significance in HC ($r_s = -0.304$, $P = 0.076$), indicating that low OXT levels correlated with high OXT reactivity to the emotional films in persons with schizophrenia.

Table 4. Group comparison of endogenous OXT's reactivity (logarithmized ratio OXT after/before film presentation) in schizophrenia patients and HCs related to the presentation of emotional *vs* control films

	Group	Gender	Test version	Group X Gender	Group X Test version	Gender X Test version
MANOVA:						
F(2,62)	4.657*	0.616	4.561*	0.874	1.593	1.024
Effect size ($_p\eta^2$)	(0.131)	(0.019)	(0.128)	(0.027)	(0.049)	(0.032)
Post hoc ANOVA:						
reactEMOI						
F(1,63)	8.208**	0.701	0.663	1.328	2.029	0.214
Effect size ($_p\eta^2$)	(0.115)	(0.011)	(0.010)	(0.021)	(0.031)	(0.003)
reactCON						
F(1,63)	2.803	0.312	7.344**	0.788	0.625	1.552
Effect size ($_p\eta^2$)	(0.043)	(0.005)	(0.104)	(0.012)	(0.010)	(0.024)

N = 35/35; MANOVA with logarithmically transformed OXT reactivities in the emotional films (reactEMOI) and in the control film (reactCON) as dependent variables; factors: group (HC/SZ), gender and test version (emotional films followed by control film/control film followed by emotional film). F[df], Effect size ($_p\eta^2$), *: $P < 0.05$; **: $P < 0.01$. Significant results are indicated in bold type.

There was no significant association of PANSS subscales with baseline OXT levels or EMOI reactivity (all $P > 0.05$), but there was a moderate negative association of OXT CON reactivity with PANSS 'general psychopathology' scores ($r_s[32] = -0.460$, $P = 0.008$). No significant associations were found between baseline OXT levels or reactivity and antipsychotic dose or duration of illness in PS or male and female PS subgroups (all $P > 0.05$).

No associations were found between baseline OXT, OXT reactivities and attachment measures (PAM anxiety and avoidance) or CTQ-SF total scores and subscales in both groups, even when analyzed separately by gender. When subjects with minimal *vs* low, moderate or severe childhood adversity (according to the cutoffs by Bernstein *et al.*, 2003) were compared, no significant differences in baseline OXT or OXT reactivity were observed in either group (all $P > 0.05$).

Discussion

Results were partially consistent with our hypotheses: (i) baseline OXT levels were significantly lower in female patients than in healthy females; (ii) OXT reactivity during emotional films, but not during control films, was significantly higher in patients compared to controls and (iii) OXT reactivity during the control video, but not during emotional films, negatively related to PANSS 'general psychopathology' scores.

Our data suggest significantly lower baseline OXT levels in female patients than in healthy women, whereas no respective differences were found between male controls and male patients. Decreased baseline OXT levels have been reported in mixed samples of patients with schizophrenia with (Goldman *et al.*, 2008) or without (Aydin *et al.*, 2018) neuroendocrine dysfunction, and in males with schizophrenia (Jobst *et al.*, 2014), while other studies reported elevated OXT levels in male schizophrenia patients (Legros *et al.*, 1992) or in samples of more than 70% males (Walss-Bass *et al.*, 2013; Strauss *et al.*, 2015) compared to HCs. No group differences (Rubin *et al.*, 2010) and no significant group x gender interactions were reported, when medicated (Rubin *et al.*, 2014) or unmedicated (Rubin *et al.*, 2013) first episode patients were each compared to HCs. Studies analyzing CSF estimated higher (Beckmann *et al.*, 1985) or similar (Sasayama *et al.*, 2012) OXT levels in patients *vs* HCs. Current evidence regarding alterations of non-induced OXT levels in psychoses is not conclusive yet and difficult to interpret due to methodological issues; gender-specific differences were not regularly considered. Of note, comparing depressed individuals with HCs, reduced baseline OXT was found in females, but not in males (Ozsoy *et al.*, 2009), and results were suggested to reflect the complex interplay between OXT and gonadal hormones with a higher sensitivity of the female OXT system to the effects of stress (Ozsoy *et al.*, 2009).

In addition, a stronger influence of antipsychotic medication on OXT pathways in female patients could be discussed. Animal studies point to a direct influence of antipsychotic drugs on OXT pathways and release (Uvnäs-Moberg *et al.*, 1992; Kiss *et al.*, 2010), though human clinical evidence is still inconclusive (Beckmann *et al.*, 1985; Sasayama *et al.*, 2012). More likely, antipsychotics cause menstrual cycle irregularities (Murke *et al.*, 2011) and thus might indirectly suppress physiological OXT fluctuations by altering the estrogen-dependent regulation of the OXT-system (Gimpl and Fahrenholz, 2001). However, some studies did not find cycle-dependent variations of OXT levels in both female patients and healthy women (Rubin *et al.*, 2010, 2011), and there were no associations between OXT measures and antipsychotic dose in our study. Altogether, the topic of neuroleptic effects on the oxytocinergic system including possible interactions with gender remains to be further explored.

OXT reactivity during emotional films, but not during control films, was significantly higher in patients compared to controls. Again, this difference was most evident in females. To eliminate the possibility of the analysis having been skewed by differing baseline OXT levels between groups, we conducted a second analysis using baseline OXT as a covariate, which did not affect our results. To our knowledge, there is only one other study of induced peripheral OXT levels during social interaction in schizophrenia (Kéri *et al.*, 2009), reporting a blunted OXT response in patients compared to controls after sharing a secret with the experimenter. Compared to an experimental setting that probably leads to rather variable emotional responses, movie stimuli in the present study can be considered to reliably elicit strong attachment-related emotions, which was confirmed for both groups by personal debriefing. However, while female patients in our study showed increasing OXT levels during the experiment, a decrease was found in healthy women. This contrasts findings in healthy individuals showing OXT level increases in subjects viewing emotionally-laden movie scenes (Barraza and Zak, 2009). Interestingly, Munro *et al.*(2013) reported

a modest rise of plasma OXT levels in females during a film's bonding scene, but its significant decrease during an abandonment scene (Munro *et al.*, 2013). Our experimental setting did not allow for differentiation of bonding and abandonment effects, as each emotional video clip contained both a bonding and an abandonment phase. Therefore, personally salient aspects of the film may have differed between diagnostic groups and led to different physiological reactions, with patients more frequently reporting an unfulfilled desire for relationship or feelings of solitude at debriefing, stating that attachment figures like the ones shown in the films were what they 'never had'. Healthy persons, who were more likely to have experienced close relationships, might have resonated more strongly with the fear of abandonment and loss. Alternatively, the 'tend and befriend' model (Taylor *et al.*, 2000) suggests an OXT release in response to stressors including social loss or threats thereof, thus increasing sensitivity and affiliative motivation (Gimpl and Fahrenholz, 2001; Onaka, 2004; Bartz *et al.*, 2011). This reaction type was found to be more prominent in women (Taylor *et al.*, 2000, 2010). As schizophrenia patients report higher personal distress when confronted with others in need, a higher susceptibility to contagion with negative emotions and reduced emotion regulation capacity (Lehmann *et al.*, 2014), film scenes of bonding and loss might cause an exaggerated experience of social stress and elicit 'tend and befriend' responses. Studies conducted in individuals suffering from depression or emotional distress suggest not only gender-specific reductions of baseline OXT (Ozsoy *et al.*, 2009), but also a dysregulated (Parker *et al.*, 2010) or more variable pulsatile OXT release (Cyranowski *et al.*, 2008). Higher OXT increases have been shown in response to relational stress (Tabak *et al.*, 2011) and in the course of an affiliation-focused imagery session, and might be related to interpersonal dysfunction (Cyranowski *et al.*, 2008). Of note, attachment-related stimuli might be more effective in eliciting OXT responses than general stress (Cyranowski *et al.*, 2008; Tabak *et al.*, 2011).

Patients' increased vigilance toward social threat may additionally stimulate OXT release (De Dreu and Kret, 2016). Brown *et al.* (2014) demonstrated a stronger tendency to avoid angry faces, as well as more severe psychotic symptoms, in schizophrenia patients with higher baseline OXT levels. Accordingly, patients in our study may have been more susceptible to the induction of fear and distress, thus exhibiting a measurable difference in OXT release compared to controls. Consistent with previous studies in healthy subjects, this effect was more prominent in females (Barraza and Zak, 2009; Taylor *et al.*, 2010). The fact that self-ratings of perceived arousal and personal relevance of stimuli did not correspond to OXT increases during EMOI may be explained by the characteristic discrepancy between autonomous arousal and experiential aspects of emotion in schizophrenia (Kring and Neale, 1996).

Although no significant associations were observed between OXT measures and self-rated attachment styles in patients in this study, attachment anxiety was significantly more pronounced in patients than in controls. Insecure attachment styles have been associated with both higher stress responses and lower mean OXT levels compared to securely bound healthy subjects (Pierrehumbert *et al.*, 2012). OXT increases in response to attachment- or trust-related stimuli were found to be most prominent in individuals with insecure attachment representations (Kiss *et al.*, 2011; Krause *et al.*, 2016). In a similar vein, our patient group scored significantly higher than HCs in almost every CTQ subscale, but no associations with OXT levels and OXT reactivities could be determined, even if gender-specific aspects and the differential impact of different types of trauma were considered. Current evidence suggests associations between adverse childhood experiences and decreased OXT levels (Heim *et al.*, 2009; Opacka-Juffry and Mohiyeddini, 2012), possibly as a result of early programming differences in OXT neurocircuitry. Stress-induced OXT concentrations have been shown to be either higher in girls having experienced sexual abuse (Seltzer *et al.*, 2014), or lower in adults with childhood sexual abuse (Pierrehumbert *et al.*, 2010). Munro *et al.* (2013) found OXT increases induced by a film's bonding scene in females with dissociative symptoms. However, we cannot exclude that differences in early childhood experience and attachment style may have modulated baseline and induced OXT levels in our patient sample, as very early interactional adversity during sensitive periods of development and disturbances of attunement and synchrony between child and caregiving persons might not be assessed by the CTQ (Feldman, 2015). Only two self-rating instruments and no objective reports were used to examine attachment representations and childhood adversity. Therefore, adverse circumstances like prematurity, maternal deprivation or maternal illness were not accounted for. Moreover, retrospective reporting might have been biased by paranoid symptoms in patients. Future research should focus on the relationship between early experience, attachment insecurity, OXT system dysregulation and psychotic vulnerability more deeply (Debbané *et al.*, 2016).

In contrast to schizophrenia patients, we observed decreased OXT levels after viewing emotional movie scenes in healthy women. Similarly, decreased OXT levels have been described as a response to negative emotional stimuli in healthy women (Turner *et al.*, 1999; Munro *et al.*, 2013). As we also observed significantly higher baseline OXT levels in female controls compared to patients, a physiological high activity of the oxytocinergic system might have attenuated reactions toward an emotional stressor. However, results regarding an association between peripheral OXT, distress or stress-related disorders are still not conclusive and 'protective' effects might be gender-specific and dependent on individual biographic factors (Taylor *et al.*, 2010; Weisman and Feldman, 2013; Olff *et al.*, 2013).

Another finding of our study was a significant main effect of test version on OXT reactivity, with higher OXT reactivity during the control stimulus, when it was presented first (test version 2). This could be due to several reasons. First, the expectation of an experimental manipulation, i.e. stress anticipation, might have impacted both experimental conditions at baseline and triggered stress-related OXT secretion (Olff *et al.*, 2013). As the EMOI stimuli on average caused higher arousal than the CON condition (Table 2), subtle stress anticipation effects might have become more obvious in the CON condition when presented first. Second, subjects in test version 1 had already watched the EMOI films, which might have lead to subsequent withdrawal of attention. Third, subjects watching the CON film first could not know that the later shown EMOI films were emotionally more impactful. Of note, watching a video about meteorological research, including diagrams and graphs, might be distressing, as indicated by significant differences in self-reports of patients and controls, and drive OXT release.

Our data do not suggest a link between baseline OXT levels and symptom severity. Previously, inverse relationships with peripheral OXT were reported for negative (Kéri *et al.*, 2009; Sasayama *et al.*, 2012; Jobst *et al.*, 2014), social, general (Rubin *et al.*, 2010) and social-cognitive symptoms (Goldman *et al.*, 2008; Strauss *et al.*, 2015), while findings regarding positive symptoms showed mixed results (Legros *et al.*, 1992; Rubin *et al.*, 2010, 2013; Brown *et al.*, 2014; Rubin *et al.*, 2014). In our patient group, a

moderate negative correlation appeared between OXT reactivity and general psychopathology in the control condition, indicating that subjects with higher OXT reactivity to emotionally neutral scenes showed less general psychopathology. It can be speculated that less symptomatic patients were more reflective, performance-oriented and therefore more prone to stress anticipation effects. However, no associations were found for the EMOI condition. Future research might rather focus on the basic principles of OXT action in schizophrenia like attribution of social salience, motivation or anxiety in a more parsimonious experimental approach (Brown *et al*., 2014).

Limitations

Limitations of our study relate to the concern that peripheral OXT levels do not reliably reflect central processes. Although some evidence suggests that stress-related OXT responses can be confined to hypothalamic or limbic regions while having no immediate effect in peripheral OXT release, a recent meta-analysis indicates a positive correlation between peripheral and CSF OXT level changes when induced by stressors (Valstad *et al*., 2017).

Moreover, no standard protocol exists for measuring OXT in blood samples. Comparability of research is hampered by the variety of (pre-)analytic procedures, but RIA with sample extraction is considered the most reliable and best-validated method (Szeto *et al*., 2011; Neumann *et al*., 2013; McCullough *et al*., 2013). Though comparability of studies is very restricted, studies using video-based emotional stimulation and enzyme-linked immunosorbent assay (ELISA; Barraza and Zak, 2009; Kéri *et al*., 2009; Munro *et al*., 2013) reported results inconsistent with ours, while RIA-based evidence regarding induced OXT levels in conditions of emotional distress (Cyranowski *et al*., 2008; Ozsoy *et al*., 2009; Tabak *et al*., 2011; Seltzer *et al*., 2014) and in healthy persons (Turner *et al*., 1999) might be less conflicting. However, research using RIA and extracted samples in patients with schizophrenia is limited to very few studies (Strauss *et al*., 2015). Until OXT assaying in humans is not standardized against methods of references of high sensitivity and specificity, interpretation of results will remain unsatisfactory (McCullough *et al*., 2013).

Another limitation of the study design refers to the fact that the time course of induced OXT release is not well known. No pilot testing of OXT peak levels was performed, but previous studies in healthy adults indicated measurable OXT increases immediately after 2 min of video-based emotional stimulation (Barraza and Zak, 2009) or after a short trust-related intervention (Kéri *et al*., 2009). To obtain a reliable emotion induction effect on the one hand and to prevent the induction of negative emotions like boredom during the control condition on the other, EMOI and CON phases were of different duration, and OXT increases during the emotional condition could therefore be not specific. In addition, it might have required more frequent measurements in timed intervals across emotion induction and recovery phases to detect group differences regarding the specific temporal dynamics of induced OXT release.

Unfortunately, neither estradiol nor prolactin as potential mediators of OXT release and their complex interactions were a focus of this study.

Further limitations refer to a possible influence of social interaction with the experimenter on OXT reactivity (Kéri *et al*., 2009), which was not systematically evaluated, the heterogeneity of the samples regarding menstrual cycle phase and the lack of control for sexual activity.

Conclusion

This study corroborates previous evidence of an alteration of the oxytocinergic system in schizophrenia by measuring peripheral OXT at baseline and after stimulation in an attachment-related experimental setting. A deeper knowledge of endogenous OXT regulation, considering its individual and biographic context and interactions with antipsychotic and mood-stabilizing agents, may forward a more personalized use of intranasal OXT as a pharmacological treatment strategy.

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7. Lebenslauf

Der Lebenslauf wird aus Datenschutzrechtlichen Gründen hier nicht angezeigt.

8. Publikationsliste

Speck, L. G., Schöner, J., Bermpohl, F., Heinz, A., Gallinat, J., Majić, T., Montag, C. (2019). Endogenous oxytocin response to film scenes of attachment and loss is pronounced in schizophrenia. *Social cognitive and affective neuroscience*, *14*(1), 109-117.

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