UNDERSTANDING SOCIAL FUNCTIONING IN SCHIZOPHRENIA

by

Cumhur Tas

A thesis submitted in partial fulfilment of the requirements for the degree of

Philosophiae Doctoris (PhD) in Neuroscience

from the International Graduate School of Neuroscience

Ruhr University Bochum

May 31st 2013

This research was conducted at the LWL University Hospital, within the Faculty of Medicine at the Ruhr University Bochum under the supervision of

Prof. Dr. Martin Brüne

Printed with the permission of the International Graduate School of Neuroscience, Ruhr University Bochum
Statement

I certify herewith that the dissertation included here was completed and written independently by me and without outside assistance. References to the work and theories of others have been cited and acknowledged completely and correctly. The “Guidelines for Good Scientific Practice” according to § 9, Sec. 3 of the PhD regulations of the International Graduate School of Neuroscience were adhered to. This work has never been submitted in this, or a similar form, at this or any other domestic or foreign institution of higher learning as a dissertation.

The abovementioned statement was made as a solemn declaration. I conscientiously believe and state it to be true and declare that it is of the same legal significance and value as if it were made under oath.

Cumhur Tas

Bochum, 07.06.2013
PhD Commission

Chair:

1st Internal Examiner: Prof. Dr. Martin Brüne

2nd Internal Examiner: Prof. Dr. Oliver T. Wolf

External Examiner:

Non-Specialist:

Date of Final Examination:

PhD Grade Assigned:
# Table of Contents

List of Figures ........................................................................................................ iv  
List of Tables .......................................................................................................... v  
List of Abbreviations ........................................................................................... vi  

Abstract .................................................................................................................. 1  

**CHAPTER 1: GENERAL INTRODUCTION** ............................................................. 3  
1.1. Definition of Schizophrenia ........................................................................... 4  
1.2. Social functioning in schizophrenia ............................................................. 4  
1.3 Neurocognition in schizophrenia .................................................................. 5  
1.4. Social cognition and metacognition in schizophrenia ............................... 6  
1.5. Learning potential and schizophrenia .......................................................... 8  
1.6. Psychosocial stress and schizophrenia ....................................................... 10  
1.7. Oxytocin: An integrative way to understand social cognition, metacognition, social functioning and social stress in schizophrenia ........................................... 12  
1.8. Aims of the thesis ......................................................................................... 17  

**CHAPTER 2-Study 1: Interconnections between metacognition, theory of mind, motivation, learning potential and their implications on social functioning in schizophrenia** ......................................................... 19  
2.1. Materials and methods .................................................................................. 19  
2.1.1. Participants .............................................................................................. 19  
2.1.2. Procedures .............................................................................................. 20  
2.1.2.1. Definition of criteria for symptomatic remission ............................... 20  
2.1.2.2. Clinical and neuropsychological measures ....................................... 20  
2.1.2.2.1. Symptomatology ........................................................................... 20  
2.1.2.2.2. Estimated general intelligence ...................................................... 20  
2.1.2.3. Metacognition and theory of mind ..................................................... 21  
2.1.2.3.1. The Indiana Psychiatric Illness Interview (IPII) ........................... 21  
2.1.2.3.2. The Metacognition Assessment Scale ........................................... 21  
2.1.2.3.3. Theory of Mind assessment .......................................................... 22  
2.1.2.4. Motivation assessment ....................................................................... 22  
2.1.2.4.1 Intrinsic motivation ....................................................................... 22  
2.1.2.4.2 Extrinsic motivation ...................................................................... 22
2.1.2.5. Perceived competency ................................................................. 22
2.1.2.6. Social functioning ................................................................. 23
2.1.2.7. Learning potential (LP) assessment .......................................... 23
2.1.2.8. Data analysis ................................................................. 24

2.2. Results ......................................................................................... 25
2.2.1. Data quality ........................................................................... 25
2.2.2. Correlational analyses ............................................................. 25
2.2.3. Between-group ANOVA ............................................................ 27
2.2.4. Multiple regression analysis ..................................................... 28
2.2.4.1. Predictors of learning potential ............................................. 28
2.2.4.2. Predictors of social functioning ........................................... 29

2.3. Discussion .................................................................................. 30

CHAPTER 3 - Study 2: Oxytocin as a predictor of social cognition training: domain specific features ................................................................. 37

3.1. Materials and methods ................................................................. 37
3.1.1. Participants ............................................................................ 37
3.1.2. Procedures ............................................................................ 38
3.1.2.1. Intervention .................................................................... 38
3.1.2.2. Social cognitive assessment .............................................. 38
3.1.3. Blood sample collection and assessment ................................. 39
3.1.3.1. Plasma oxytocin assessment .............................................. 39
3.1.5. Data Analyses .................................................................... 40

3.2. Results ......................................................................................... 41
3.3. Interim Discussion ...................................................................... 43

CHAPTER 4 - Study 3: Cortisol response to stress in schizophrenia: associations with oxytocin, social support and social functioning ................................................................. 48

4.1. Materials and methods ................................................................. 48
4.1.1. Participants ............................................................................ 48
4.1.2. Procedures ............................................................................ 49
4.1.2.1. Symptomatology ............................................................... 49
4.1.2.2. Social functioning assessment ........................................... 49
4.1.2.3. Social isolation assessment ............................................... 50
4.1.2.4. Perceived stress evaluation ............................................... 50
4.1.2.5. Psychosocial stress test ..................................................... 50
List of Figures

Figure 4.1: Means (and standard errors) illustrating the change of cortisol levels after the social stress induction, with a group split of cortisol responders and non-responders .......... 54

Figure 4.2: Box plot of oxytocin levels for each subject within cortisol responder and non-responder groups to psychosocial stress ................................................................. 55

Figure 4.3: Scatter plot between the oxytocin levels and the cortisol reactivity index .......... 56

Figure 5.1: An integrative model to understand social functioning in schizophrenia .......... 74
List of Tables

Table 2.1: Inter correlations among the variables ............................................................. 26
Table 2.2: ANOVA between-group analysis of learning categories ...................................... 27
Table 2.3: Hierarchical regression analysis for predicting learning potential ........................ 29
Table 2.4: Pearson correlation analyses among the independent predictors and social
functioning subdomains ..................................................................................................... 30
Table 3.1: Sociodemographic and clinical variables ............................................................ 38
Table 3.2: Mean outcome variables ..................................................................................... 41
Table 3.3: Correlation analyses between the predictors of interest and social cognition gain
scores .................................................................................................................................. 42
Table 3.4: Predictors of improvement in social cognition tasks after the training ............... 43
Table 4.1: Sociodemographic and clinical variables ............................................................ 49
Table 4.2: Curvilinear regression results between oxytocin and cortisol reactivity ............ 56
Table 4.3: Group difference on measures of trait anxiety, social support and social
functioning ........................................................................................................................ 57
Table 4.4: Inter-correlations among the behavioural measures derived from the different
scales and the endocrine measures .................................................................................... 59
Table 4.5: Predictors of social functioning .......................................................................... 61
Abbreviations

ToM: Theory of Mind
SDT: Self Determination theory
EM: Extrinsic Motivation
IM: Intrinsic Motivation
LP: Learning Potential
CVLT-II: California Verbal Learning Test—II
WCST: Wisconsin Card Sorting Task
HPA: Hypothalamic–pituitary–adrenal
CRH: Corticotrophin releasing hormone
AVP: Arginine-vasopressin
ACTH: Adrenocorticotropic hormone
PFC: Prefrontal cortex
TSST: Trier Social Stress Test
PVN: Paraventricular nucleus
SON: Supraoptic nucleus
CSF: Cerebrospinal fluid
ELISA: Enzyme-linked immunosorbent assay
CPZ: Chlorpromazine equivalent dosages
PANSS: The Positive and Negative Syndrome Scale
MQ: The memory quotient
MAS: Metacognition Assessment Scale
PCS: Perceived Competency Scale
SFS: Social Functioning Scale
IMI-SC: Intrinsic Motivation Inventory for Schizophrenia.
MC: Metacognition
SWL: Social withdrawal
IPL: Interpersonal relationship
PSA: Prosocial activities
RC: Recreation
IND/CP: Independence/Competence
IND/PER: Independence/Performance
OCP: Occupation/Employment.
CRT: Cognitive remediation training
F-SCIT: Family-assisted social cognition and interaction training
EP: Emotion perception
FEIT: Face Emotion Identification Task
FEDT: Face Emotion Discrimination Task
RMET: Reading-the-Mind-in-the-Eyes Test
PB: Personalization bias
EB: Externalization bias
IPSAQ: The Internal, Personal, and Situational Attributions Questionnaire
MOC; Medical Outcomes Study Social Support Survey
CR: Number of close relationship
TS: Tangible support.
EIS: Emotional or informational support.
AS: Affectionate support.
PSI: Positive social interaction support.
QoL: Quality of life
SAD: Social anxiety disorder
The presence of deficits in social functioning is one of the hallmark characteristics of schizophrenia. Up until today, numerous factors such as symptom severity, neurocognitive impairments, and social cognitive deficits have been attributed to the social impairments seen in schizophrenia patients. However, it is still not clear whether the aforementioned factors may totally explain the heterogeneous nature of social behavior in schizophrenia. Besides this, there appears to be a gap between clinical and biological studies, which results with a large body of literature waiting to be harvested. Nowadays, metacognitive deficits in schizophrenia together with the neuropeptide oxytocin have become potential factors of interest to address this gap. Accordingly, the aim of the present thesis was to study the effects of metacognition, plasma oxytocin levels, and cortisol response to social stress on social impairments in schizophrenia. Three studies based upon the following fourfold hypothesis were conducted: 1) Metacognitive deficits are associated with theory of mind deficits but also have distinct features over domains such as intrinsic motivation in schizophrenia. 2) Metacognitive deficits can predict some variance in social functioning and learning in schizophrenia. (3) Considering the stress regulating effects of oxytocin, and the heterogeneous nature of schizophrenia, a group of patients with intact neuroendocrine response to stress could present higher social functioning. (4) Considering the ample evidence, which suggests that oxytocin enhances the perception of basic emotional cues, the effects of baseline plasma oxytocin levels could influence training-based improvements in emotion perception for schizophrenia patients. Accordingly, these studies were conducted on clinically stable schizophrenia patients. Self-report measures of social functioning, social support, intrinsic motivation, self-competency, perceived anxiety were collected in addition to a test battery of social cognition. An experimental cognitive remediation training was utilized for the first study. The widely used Trier Social Stress Test was performed to induce stress in the third study. Blood samples were collected to measure oxytocin and cortisol levels for this study. Lastly, to answer the fourth hypothesis, a structured social cognition and interaction training was performed in which blood samples were collected to measure baseline oxytocin levels. According to the results, although some with small effect sizes, the hypotheses were generally accepted. It was shown that patients’ metacognition had substantial potential to explain learning capacity, intrinsic motivation, and social functioning.
in schizophrenia. Moreover, cortisol reactivity to social stress, together with basal cortisol levels and social support, predicted social functioning. Patients below the median cortisol reactivity indices presented lower oxytocin levels, although it appeared that this relationship was not linear. Lastly, plasma oxytocin levels in schizophrenia predicted the treatment outcome of the emotion discrimination part of the social cognition training. Understanding social functioning in schizophrenia is crucial for developing new treatment strategies that are beneficial for our patients. On the way to recovery in schizophrenia, there does not appear to be a magic bullet, but the aforementioned domains may hopefully help us to develop individualized psychosocial and psychopharmacological treatment strategies based on the patient’s metacognitive, social cognitive and neuroendocrine regulation capacity.
CHAPTER 1

GENERAL INTRODUCTION

“The peculiar destruction of the inner coherence of the psychic personality with dominant damage of the emotional life”

- Emil Kraepelin’s definition of Schizophrenia

Preamble

Schizophrenia is a chronic, recurrent, severe mental disorder, which is accompanied by serious deficits in social functioning. Since Eugen Bleuler suggested the core symptoms of this group of disorders as being potentially remittable, therapeutic efforts have focused on social functioning, quality of life and recovery as important targets (Lysaker et al., 2010b). Nowadays, a substantial amount of research focuses on potential functional recovery that includes the remediation of social problem-solving skills and social functioning, although limited success has been accomplished up until today (Kurtz et al., 2010; Wykes, 2008).

In the past, studies exploring the potential predictors of poor social functioning in schizophrenia have highlighted two main underlying factors, namely neurocognition and symptomatology (Andreasen et al., 2005). Though more recently, social cognition, which is the set of cognitive processes applied to the recognition, understanding, accurate processing, and effective use of social cues in real-world situations, emerged as a critical domain to predict the social dysfunction of individuals with schizophrenia (Brüne et al., 2007). In addition to social cognition, metacognition, which is an umbrella term that covers a set of social cognitive capacities filtered by neurocognitive processes, has been proven to be closely related with the overall course of the illness (Lysaker et al., 2005).

Schizophrenia is a prototypical brain disorder that both affects and is affected by the social environment. Although existing models cover a fair amount of ground in explaining social functioning in schizophrenia, the contribution of recent developments in the field of neuroscience have expanded our knowledge, not only by evaluations at the cognitive level, but also at the biological level. So far, there has been a gap between cognitive neuroscience and the field of psychiatry, possibly due to different hypothetical research questions, which has led to a lack of continuum between cognition and real-world functioning in
schizophrenia. Thus, this thesis seeks to find a more integrative approach by considering the neurobiology of human social interaction and social performance, and how these are blended together with social cognitive processes. By virtue of this proposal, the main focus of this thesis is to try to answer these uncertain questions related to the social functioning of patients with schizophrenia.

1.1 Definition of schizophrenia

Schizophrenia is a chronic mental health disorder with a prevalence rate of 0.5 to 1 percent. It is considered as a multifactorial disease, which involves multiple genes and environmental factors. The first onset of schizophrenia usually occurs at the age of 18-25 years and is often preceded by premorbid behavioral deviations, such as social withdrawal and blunted affect (Sadock et al., 2007). According to the “vulnerability-stress model” (Yank et al., 1993), besides the genetic background, stressful life events and environmental factors such as intrauterine and prenatal complications, other organic diseases, poor social environment, and inadequate coping skills for the recognition and management of life events can contribute to the development of schizophrenia (Sadock et al., 2007).

The diagnosis of schizophrenia is based on the presence of symptoms as defined in diagnostic systems. The symptoms of schizophrenia are commonly divided into two clusters, namely positive symptoms and negative symptoms (Sadock et al., 2007). Hallucinations, delusions and disorganized behavior are types of positive symptoms, whereas negative symptoms are characterized by the deterioration of “normal” functioning. Negative symptoms in schizophrenia consist of flattened affect (e.g. blunted emotions), avolition (lack of initiative), anhedonia (loss of pleasurable feelings), and social withdrawal (Sadock et al., 2007). There has previously been some debate in the literature as to whether or not negative symptoms also include cognitive deficits such as “attention problems” in schizophrenia (Green, 1996). Today, numerous studies indicate that cognitive deficits should be regarded as a core independent domain in schizophrenia (Addington and Addington, 2000; Ventura et al., 2009).

1.2. Social functioning in schizophrenia

Deficits in social functioning are more pronounced in schizophrenia than in most other major psychiatric disorders. Ample research has repeatedly reported that almost 75% percent of individuals with schizophrenia show social impairments over one year (Mueser et
al. 1991). In general, deficits in social skills pave the way before the illness onset, persist following the first psychotic attack, and show progressive deterioration. Importantly, impairments in social functioning are significant predictors of outcome, such as the number of relapses, the severity of the illness course, and occupational status (Addington and Addington, 1999; Brekke et al., 2005)

Social functioning in schizophrenia has also implications on the well-being of the patients. The vast majority of patients report having few close friends, lack of positive social interaction and low life satisfaction (Brissos et al., 2011; San et al., 2007). Patients consistently report improvements on social functioning as a treatment objective. For instance, schizophrenia patients rated social functioning as their area of highest unmet need in a thought-provoking study (Bengtsson-Tops and Hansson, 1999). Taken as a whole, understanding and focusing on social functioning may directly address fundamental human needs and hence improve well-being.

1.3 Neurocognition in schizophrenia

Following the consistent findings on the critical role of deficits in social functioning, researchers have shown extensive interest in the factors that can explain social impairments in individuals with schizophrenia. Neurocognitive deficits emerged as a critical area of study in this regard. Today, extensive literature data presents a significant relationship between various indices of neurocognition (e.g., attention, working memory and executive functioning) and social impairments in schizophrenia (Addington and Addington 1999; Bell and Mishara, 2006). However, the amount accounted for variance is typically modest (around 40-60 percent) and therefore suggests that a considerably large amount of the social deficits appears to be explained by other factors (Green, 1996; Penn et al., 1997b).

Counterintuitively, this has led researchers to draw their attention away from neurocognition to other related but distinct aspects of human cognition, which can independently account for social functioning in schizophrenia. Thus, the study of social cognition was born and dominated the field of studies of psychosocial interventions, social functioning and quality of life in schizophrenia (Penn et al., 1997a).

1.4 Social cognition and metacognition in schizophrenia
The human capacity for social interaction is a complex phenomenon that has become the focus of social neuroscience in the last decade. Recently, a large number of studies have underlined the cognition involved in the perception and processing of social signals, namely “social cognition” as another domain that is impaired in schizophrenia (Green et al., 2008).

Social cognition is “a set of cognitive processes applied to the recognition, understanding, accurate processing, and effective use of social cues in real-world situations” (Harvey and Penn, 2010). Ample evidence indicates that brain correlates of neurocognition are dissociable from those of social cognition by a large extent (Green et al., 2008; Adolphs 2006, 2010). There is accumulating evidence that suggests the presence of a neural network encompassing the amygdala, fusiform gyrus, superior temporal sulcus, and prefrontal cortex (Adolphs, 2003; Pinkham et al., 2003) that is particular for social cognitive processes.

Recently, researchers studying social cognition arrived at a consensus on three key sub-domains that most commonly present deficits in schizophrenia (reviewed in Brown et al., 2012). These sub-domains are emotional processing, attributional bias, and theory of mind (ToM). Emotional processing deficits in schizophrenia consist of several impairments such as the recognition of emotions on the face, emotion discrimination, and emotion perception. In “real-world” settings, recognizing and correctly interpreting facial emotional expressions is the initial step for successful social interaction (Pinkham et al., 2008). Addington et al. (1998) demonstrated a direct relationship between impairments in facial emotion recognition, negative symptoms, and social functioning in schizophrenia. Deficits in emotion perception had substantial influence on other impaired domains of social cognition (Green et al., 2008). By and large, a substantial number of studies reported a relationship between emotional processing and deficits in attributional bias and theory of mind (Green et al., 2008). By definition, theory of mind refers to the ability to represent other people’s thoughts and intentions in our own mind (Brüne, 2005). Studies found that theory of mind deficits exist not only in first-episode and remitted schizophrenia patients but also in a group of subjects who are at risk of developing schizophrenia (Gibson et al., 2010). In the past, there has been a debate on whether theory of mind deficits dependent on neurocognition. However, today ample evidence demonstrated that they are independent with also distinct neuroanatomical correlates (Brüne, 2003). Lastly, attributional bias refers to the tendency to whether negative or positive situations are causally attributed to oneself or to others (Green et al., 2008). In brief, healthy people take advantage of externalizing bias as a self-serving bias under negative circumstances. However, studies in schizophrenia patients demonstrated an over-
self-serving bias which in turn triggers delusional formation and paranoid thoughts (Humphreys and Barrowclough, 2006; Langdon et al., 2010).

An ever-growing body of literature indicates that particularly emotion perception and ToM are closely related to social functioning in schizophrenia (Horan et al., 2011a; Leitman et al., 2006; Mazza et al., 2010). Furthermore, some of these studies have demonstrated a stronger relationship of ToM with social functioning than neurocognition (Brüne, 2003; Brüne et al., 2007). Equally interesting is that, such strong relationship was more apparent when the functional outcome evaluations were based on performance-based scales that are close to “real-world” settings (Bell et al., 2009; Harvey et al., 2011). Other studies have shown that neurocognitive faculty does not affect the relationship between social cognition and functional outcome, although these domains appear to make independent contributions to social dysfunction in patients with schizophrenia (Fett et al., 2011). Recently, Couture et al. (2011) demonstrated with a path analysis method that the model, which includes social cognition as a mediator between neurocognition and social functioning, can best explain their relationship in a large schizophrenia sample. Taken together, this large body of literature indicates the indispensable role of social cognition on functioning.

Nowadays, "the knowledge and cognition about a cognitive phenomenon" (Flavell, 1979), referred to as metacognition, turned out to be another area of interest in schizophrenia studies. It was first described as the memory processes with metacognitive operations, although studies have recently investigated some other faces of metacognition that are more related to the human social life (Semerari et al., 2003). In fact, the terms “Metacognition,” "Mindreading," “Theory of Mind,” and “Mentalizing” refer to a person’s general capacity to think about thinking, both their own thinking and the thinking of others (Adolps, 2006; Semerari et al., 2003). Although these terms are often used in an interchangeable manner to refer to a general ability, they involve a wide range of partially independent faculties that allow persons to form representations of their own mental states and the mental states of others (Lysaker et al., 2011a). These capacities allow humans to resolve their own problems, to understand another’s intentions, and lastly to ultimately adapt to a novel social environment (Dimaggio et al., 2008).

In schizophrenia, substantial amount of research has demonstrated that metacognitive deficits are associated with the course of illness, independent of symptomatology and neurocognition. Metacognitive deficits in schizophrenia are related to the capacity to monitor one’s own thinking and behavior, to mentalize and to form complex ideas of one’s own life (Lysaker et al., 2005). Recently, Lysaker and his research group presented ample evidence
that these deficits are closely related with social impairments (reviewed in Brüne et al., 2011). They have demonstrated that metacognitive skills in schizophrenia were related with symptom severity (Lysaker et al., 2005), neurocognition (Lysaker et al., 2010c), work performance (Lysaker et al., 2010a), social interaction (Lysaker et al., 2011b), insight, self-esteem (Lysaker et al., 2011a), social anxiety (Lysaker et al., 2011a) and social cognition (Lysaker et al., 2013) in schizophrenia. Moreover, they evaluated the continuum of metacognitive deficits in a longitudinal study, which was found as relatively stable (Lysaker et al., 2010a). Most recently, metacognitive deficits were also present in individuals with high risk for developing schizophrenia. For instance, young individuals with a risk of developing schizophrenia were followed up in a longitudinal study (Barbato et al., 2013). Accordingly, individuals who developed schizophrenia had lower metacognition scores at the pre-onset.

Furthermore, understanding one’s own mental state and those of others may also contribute to one’s motivational drives. The effects of metacognitive awareness on motivation was first pronounced in Deci and Ryan’s Self Determination theory (SDT), which describes motives under situations as a continuum, with intrinsic motivation (IM) at one end and extrinsic motivation (EM) at the other (Deci and Ryan, 1985). SDT indicates that the fundamental difference between IM and EM is that the former refers to doing something because it is inherently interesting or enjoyable, whereby the latter refers to doing something because it leads to a separable external positive outcome. These two distinct domains are integrated with each other, with self-regulation and self-awareness (Deci and Ryan, 2000). Notably, the role of metacognition on the intrinsic motivation of schizophrenia has not been studied in schizophrenia. Taken as a whole, there is a growing evidence that schizophrenia patients struggle not only because of symptoms and neurocognitive impairments, but also because of difficulties in regulating their behavior, as well as interpreting and making sense of the their own dilemmas, which consequently may impact on variables such as motivation and social functioning.

1.5. Learning potential and schizophrenia

In addition to deficits in metacognition and social cognition, an individual’s neurocognitive amelioration, so-called the learning potential (LP), was pronounced as another predictor of social functioning in schizophrenia. LP is typically measured dynamically through repeated test administrations, in a pretest-intervention/training-post-test sequence rather than a single test administration (Fiszdon and Johannesen, 2010). Several studies have
suggested that LP mediates the relationship between neurocognitive performance and social functioning in schizophrenia (Sergi et al., 2005; Vaskinn et al., 2008; Woonings et al., 2003). Kurtz et al. (2010) demonstrated that a dynamic assessment of cognition with learning potential with the California Verbal Learning Test—II (CVLT-II; Delis et al., 2000) and the Wisconsin Card Sorting Task (WCST) has potential to explain social dysfunction in schizophrenia. They found a moderate correlation between neurocognition and LP, although this failed to explain the variance attributed to social functioning. Another study looking for neurocognitive predictors of readiness for psychosocial rehabilitation in schizophrenia reported that a group classification based on learning potential predicted performance in both standard and explicit training in semantic memory (Fiszdon et al., 2006).

Eventually, the term “LP” sticks around the remediation of cognitive functions above and beyond a person's manifest performance (e.g., Sternberg and Grigorenko, 2002). Alongside the efforts to explain the role of neurocognition in learning potential, only a few studies have directly investigated the psychological motives that drive individuals to learn better from a specific training or life experiences. For example, several studies in educational psychology argued that the LP of an individual is mediated by the metacognitive performance (e.g. McCabe, 2011). In essence, metacognition can influence LP through self-regulated learning, which is the learning that involves autonomy through self-monitoring and self-regulation of the goals of information acquisition and self-improvement (Kuiper and Pesut, 2004; Swanson et al., 1996).

For instance, participants who had the higher learning capacity typically also displayed high metacognitive skills yet with adequate (not extreme) perceived anxiety while performing a cognitive task (Beer et al., 2012; Tobias et al., 1997). Moreover, though not accounting for metacognition, previous studies proposed an inverted u-shaped relationship between the learning and the task-related stress of the participants (Cahill et al., 2003; Richter et al., 1998). Accordingly, not only extreme amounts but also the lack of perceived anxiety negatively impacts on learning potential and the performance (Joels et al., 2006). Taken as a whole, it is plausible to argue that the perceived stress that mediates the individuals’ task-related performance is modulated by the metacognitive skills of individuals who were exposed to the task. However, much further work is needed here to tease apart the different effects and to understand its implications on patients who present impaired learning capacities such as schizophrenia.
1.6. Psychosocial stress and schizophrenia

Stress is a psychosomatic event and is changeable by intensity and duration among individuals. It is usually triggered by certain external and internal conditions (stressors) (Erdmann et al., 1984; Janke and Amelang, 1965; van Eck et al., 1996) and is an adaptive response to maintain the homeostasis of the organism. The neuroendocrine stress response of vertebrates, particularly mammals, is activated by the hypothalamic–pituitary–adrenal (HPA) axis (Fink, 2007). Accordingly, the HPA axis is first triggered by the excitation of the paraventricular nucleus neurons, which synthesize corticotrophin releasing hormone (CRH), and arginine-vasopressin (AVP) in the hypothalamus (Fink, 2007). CRH and AVP pass via the blood into the anterior pituitary gland and stimulate the synthesis and secretion of adrenocorticotropic hormone (ACTH) (Herman and Cullinan, 1997). ACTH then activates the adrenal cortex, which releases cortisol. The HPA axis is controlled by cortisol levels in the blood which leads to a negative feedback loop to inhibit the release of CRH and ACTH in the hypothalamus and the pituitary gland (Sapolsky et al., 2000).

The HPA axis is responsible for important physiological reactions that are necessary for adaptation to stressful situations. The main features of the HPA response to stress can be stated as follows: Firstly, cortisol mobilizes energy consumption of the body by increasing the blood glucose (Gonzalez-Bono et al., 2002). Secondly, activities of epinephrine, norepinephrine and dopamine are also partially regulated by the cortisol levels (Chrousos and Gold, 1992; Pruessner et al., 2004). A weak or a strong HPA response with a rapid change in the hormone levels enables the organism to supply the necessary energy to overcome a burden (Chrousos, 1992). On the contrary, a prolonged elevated cortisol level is associated with adverse effects, such as suppression of the immune system and the development of chronic physical and mental health diseases (e.g. DeRijk et al., 1997). Thirdly, the activity of the HPA axis influences the cognitive and affective processing streams both in the positive and negative direction (Dickerson and Kemeny, 2004). For instance, brain areas which are involved in information processing such as the hippocampus and the medial prefrontal cortex (PFC) have afferents throughout the HPA axis, thus suggesting a strong link between the neurocognitive faculty and the stress regulatory systems (e.g. Figueiredo et al., 2003; Herman et al., 2003; Wolf, 2009).

In human studies, there are two standardized methods to induce neuroendocrine stress responses under laboratory conditions: first by utilizing physiological and second by psychological stimuli (Dickerson and Kemeny, 2004). The physiological methods are those...
which have a direct influence on the physiological processes of the HPA axis. These methods include for example inhalation of CO2, induction of pain, heat or cold, and pharmacological manipulation of the HPA axis (LeBlanc et al., 2004; Lupien et al., 1999; McMorris et al., 2006; Schwabe et al., 2008; van Stegeren et al., 2008). On the other hand, the psychological stressors affect physiological stress by activating affective and cognitive processes associated with the brain structures that are interconnected with the HPA axis (reviewed in Foley and Kirschbaum, 2010). The main difference between the psychological and physiological stressors is the “appraisal” effect of stressors, meaning the interplay between the individual and the environment. In other words, an individual’s estimation of a stimulus as being stressful is essential for triggering the neuroendocrine response for the psychological methods, whereas the investigator capitalizes on the direct biological pathways to induce a neuroendocrine stress response in the physiological methods. Although the psychological type of stress induction may be less robust than the physiological stressors, their influence on the HPA axis is more similar to real-world settings, and hence received higher priority on the field of stress research in the last couple of years (Biondi and Picardi, 1999; Dickerson and Kemeny, 2004; Kudielka et al., 2004b)

Kirschbaum and colleagues have extensively studied the stress-induced endocrine response using a psychosocial stress paradigm, referred to as the “Trier Social Stress Test” (TSST) (Kirschbaum and Hellhammer, 1989; Kirschbaum et al., 1993; Kudielka et al., 2004a). The TSST is a standardized psychological stress test that alters the concentrations of ACTH, cortisol and prolactin levels during the experimental procedure. The TSST contains all the terms and features that promote a strong activation of the HPA axis, such as social assessment, uncontrollability, novelty, unpredictability, and the combination of a verbal interaction with a cognitive task (Dickerson and Kemeny, 2004). The implementation of the TSST is standardized: the subjects are first instructed to perform a job interview to prove why they are the best candidate for a position corresponding to the desired occupation of the subject in front of a committee which consists of three interviewers. Participants are left in a room for 10 minutes to prepare themselves for the performance part. Right after the preparation part, the subjects perform a 5-minute free speech about themselves. This standard procedure is followed by a 5-minute mental arithmetic task. The subjects speak during the task into a microphone and are filmed with a video camera. They are also told that that the committee is trained in behavioral observation. Notably, the behavior of the committee is serious and neutral-to-negative. There should be no affirmative or supportive gestures or comments and only stereotypical responses are allowed. Following the performance part, one
of the experimenters gives 10 minutes of debriefing. The purpose of this last part is to calm
down the behavioral stress response of the participants and to normalize things again
(Kirschbaum et al., 1993).

In general, studies in various psychiatric populations performing the TSST have
revealed that symptom severity and poor social functioning are associated with higher basal
hypothalamic-pituitary-adrenal (HPA) activity (de Timary et al., 2008; Petrowski et al., 2010;
Walder et al., 2000), yet with attenuated cortisol responses (Errico et al., 1993; King et al.,
2006; Pruessner et al., 2013; Wamboldt et al., 2003). One typical contrasting finding coming
from studies conducted on socially anxious individuals is the supranormal cortisol reactivity
following the TSST (Elzinga et al., 2010; Hoge et al., 2013; Tyrka et al., 2007). An
attenuated or absent cortisol response has also been demonstrated in people with
schizophrenia (e.g. Meltzer et al., 2001). Brenner et al. (2009) found that schizophrenia
patients had a non-significant cortisol response to stress, despite a significant increase in heart
rate and blood pressure, whereas the cortisol levels of healthy controls significantly increased
by approximately 35-45% relative to baseline after the TSST. Other studies have also
revealed a selective response to stress in which schizophrenia patients had a normal
autonomic response, but an absent increase in cortisol levels (Jansen et al., 2000). To the best
of knowledge, only one study (Brenner et al., 2011) has addressed the potential behavioral
implications of cortisol responses in schizophrenia, in which the attenuated cortisol response
to social stress (elicited by the TSST) was surprisingly associated with greater quality of life,
as indicated by perceived life satisfaction.

As mentioned above, schizophrenia is characterized by impaired social functioning
but also by problems in adapting to socially stressful environments. Adaptation of the self,
following stressful life events is critical for social functioning (Allman, 1999). Erikson
(1968), in his psychosocial development theory, suggests that a failure in this reorganization
may result in maladaptive behavior such as social withdrawal or passivity symptoms. Taken
together, cortisol reactivity to social stress may further help us to expand our understanding
of social functioning in schizophrenia.

1.7. Oxytocin: An integrative way to understand social cognition, metacognition, social
functioning and social stress in schizophrenia

A sufficient physiological and behavioral response to acute social stress is essential to
successfully cope with the hassles of daily life (Engelmann et al., 2004). The initial endocrine
response to an event that is appraised as stressful promotes the activation of required cognitive faculties, increases heart rate to certain levels, which meets the physical and emotional demands to react to the stressor and prepares the organism to have a delicate balance between the approach and avoidance tendencies (Engelmann et al., 2004). Animal and human studies have extensively investigated the effects of the social environment on stress coping mechanisms. For instance, exposure to social isolation was interconnected with decrements in neurocognitive functioning, impairments in stress regulation and inappropriate aggression (Ma et al., 2011; Pinna et al., 2004). Considering also that social isolation is a phenomenon that patients with schizophrenia often experience (van Os et al., 2000), not only neurocognition, social cognition and metacognition, but also biological factors associated with social isolation can be informative to fully grasp how social functioning is driven in schizophrenia. Today, accumulating evidence has stressed oxytocin and glucocorticoid activity as two main biological predictors of this phenomenon (Hennessy et al., 2009).

The neuropeptide oxytocin was first discovered in 1909 by a histology study that analyzed the pituitary gland extracts. The magnocellular and parvocellular neurons of the paraventricular nucleus (PVN) and the magnocellular neurons of the supraoptic nucleus (SON) of the hypothalamus are responsible for the storage and synthesis of oxytocin (Neumann and Landgraf, 2008). In human studies, researchers utilized four main methods to study the effects of oxytocin (Heinrichs et al., 2009). The first method is by measuring the brain levels of oxytocin: In this approach, cerebrospinal fluid (CSF) is collected through a lumbar puncture and the biochemical analyses are conducted on the collected sample. Today, this approach is rarely used due to its invasive procedure with high side effects. However, several human studies in the 1980s demonstrated significant correlations between CSF levels of oxytocin and psychopathology, emotion perception and childhood trauma (Amico et al., 1983; Demitrack et al., 1990; Leckman et al., 1994; Raskind et al., 1986). Nevertheless, a recent study in schizophrenia patients found significant negative correlations between the negative symptoms and the (CSF) oxytocin levels (Sasayama et al., 2012). The second method is, by physiological stimulation: An adequate number of studies evaluated the effects of endogenous oxytocin levels on human social behavior through physiological stimulations, which are known to secrete oxytocin from the hypothalamus. For example, nipple stimulation or lactation in female subjects are well-known methods to increase the release of oxytocin into the circulatory system (Chatterton et al., 2000; Hatjis et al., 1989; Uvnas-Moberg, 1998). However, the main limitation of this approach is the fact that it is prone to high inter-subject
differences and cannot be easily standardized. The third method is by plasma oxytocin assessment: numerous studies showed reliable and replicable findings using enzyme-linked immunosorbent assay (ELISA) methods and evaluating the plasma oxytocin levels in humans (McCullough et al., 2013). Oxytocin has a very short half-life (i.e. 6-8 minutes), and once it is secreted from the central nervous system, only 1% of it can pass through the blood-brain barrier again. Therefore, in the last couple of years, there has been a debate over the reliability of the samples collected from plasma. However, recent studies demonstrated that these discrepancies mostly occurred due centrifuge and plasma extraction techniques which were utilized to measure plasma oxytocin levels (McCullough et al., 2013; Szeto et al., 2011). Despite these discrepancies, accumulating evidence suggests that plasma oxytocin measurement is a reliable measure and correlated with various behavioral and cognitive measures (Bertsch et al., 2013; Gossen et al., 2012; McCullough et al., 2013; Pierrehumbert et al., 2012; Weisman et al., 2013).

The fourth method is by nasal administration of oxytocin: Today, this approach has received much popularity due to its high feasibility and standardization (Heinrichs et al., 2009). Most of the recent studies administered intranasal oxytocin to explore the effects of the oxytocinergic system on social behavior, social cognition, and social stress, and found consistent and well-replicable results (reviewed in Heinrichs et al, 2009). One main drawback of this approach is the lack of knowledge of the endogenous oxytocin levels of the subjects before the administration. It is plausible to argue that subjects with different levels of basal oxytocin may cognitively or behaviorally respond to external administration in a slightly different manner. Along the same line, recent evidence presented a dose-dependent effect of intranasal administration (Cardoso et al., 2013).

Nowadays, the role of oxytocin on the regulation of the HPA axis is under serious investigation. The theory behind such effects lies under the so-called social buffering hypothesis, which argues that communication and interpersonal relationships are essential for mammalians not only for exchanging necessary information but also to smoothly recover from an experience of distress (Hennessy et al., 2009). Evidence up until today suggests that during psychological stress, oxytocinergic neurons in the PVN are activated and subsequently release oxytocin. The neurobiology of social buffering states that the secreted oxytocin has three main pathways (Neumann et al., 2000): 1) the glucocorticoid pathway: Oxytocin inhibits the HPA axis activation in several steps through this pathway (Neumann et al., 2000). For instance, oxytocin secretion through female nipple stimulation in females has been shown to be accompanied by a decrease in plasma cortisol levels (Amico and Finley, 1986; Finley et al., 1986). Another study found that ACTH release from the pituitary gland was inhibited by
an increase in peripheral oxytocin after lactation in a group of female participants (Slattery and Neumann, 2008). Such inhibition of the HPA axis through oxytocinergic circuits also occur at the hypothalamic level as concluded in an adequate amount of work. For instance, Windle et al. (2004) demonstrated that intraventricular injection of oxytocin attenuated the corticotrophin releasing factor (CRF) mRNA responses to physical stress in rat models (Windle et al., 2004; Windle et al., 1997). 2) The opioid pathway: Oxytocin neurotransmission also leads to the release of opioids, which have known properties not only on anti-stress mechanisms but also on the rewarding features of social interaction (Bell et al., 2006; Rilling et al., 2011). Lastly, 3) The activation of the central oxytocinergic system increases the dopaminergic activity in the nucleus accumbens, which in turn again activates reward-related processes during interpersonal relationships (Lim et al., 2005; Skuse and Gallagher, 2009).

To the best of knowledge, the first work that studied the effects of oxytocin on social stress was conducted by Heinrichs and his colleagues in 2003. They found that administration of oxytocin before the TSST suppressed the cortisol reactivity to the social stress. They further reported a group of participants who received social support in the preparation phase of the TSST had also lower cortisol reactivity following the performance part of the TSST. In another study, peripheral levels of oxytocin were collected before and after the TSST (Fekete et al., 2011). After the performance part, researchers demonstrated that subjects who had lower plasma oxytocin levels at baseline also presented a lower cortisol response to stress, which was attributed to the buffering effect of oxytocin over cortisol response. An indirect support to this finding came from another study, which found that subjects with a history of emotional abuse had the highest increase of plasma oxytocin after the TSST (Pierrehumbert et al., 2012). Equally interesting, the same study also described a group of participants with cancer history in their childhood exhibiting a higher oxytocin increase after the TSST when compared to healthy controls. Researchers attributed such dynamic increase of oxytocin levels to its regulatory effects on cortisol reactivity to stress. In other words, an increased oxytocinergic activity was triggered by the assumption of corrupted HPA axis due to traumatic childhood history in the Pierrehumbert et al. study. Taken together, it is clear that oxytocin facilitates stress regulation but little is known about individual differences in this effect. For instance Quirin et al. (2011) administered oxytocin to a group of participants which they measured emotion recognition capacities in addition to their cortisol response to the TSST. They found an improvement in the recognition of emotions following the attenuation of cortisol response to stress after oxytocin administration only in the group who
present higher deficits in emotion recognition at baseline. Lastly, a recent study found that intranasal administration of oxytocin attenuate cortisol response to stress (Cardoso et al., 2013). Critically, they found a dose-dependent effect of oxytocin on cortisol response, because the inhibitory effect over the HPA axis was only observed with low dose administration but not high.

With respect to schizophrenia, oxytocin has been shown to have some influence on symptom severity (Sasayama et al., 2012; Rubin et al., 2010), social cognition (Averbeck et al., 2011) and trust behavior (Keri et al., 2009). In addition, oxytocin as an adjunct treatment to standard antipsychotic medication has the potential to reduce both positive and negative symptoms (Feifel, 2012), improve verbal memory (Feifel et al., 2012) and theory of mind in schizophrenia (Pedersen et al., 2011). Recently, social perception has been found to be altered by oxytocin administration in a group of schizophrenia patients but not in healthy controls (Fischer-Shofty et al, 2013). More recent and comprehensive interpretations of the effects of oxytocin on cognition and symptom severity in schizophrenia emphasize its anxiety-reducing and affiliation-propagating properties (reviewed in Meyer-Lindenberg et al., 2011). However, the associations between the oxytocin levels and cortisol reactivity to psychosocial stress and their impact on social functioning in schizophrenia have not been studied up until today. Moreover, considering the commonly replicated finding of attenuated cortisol response to social stress in schizophrenia and the heterogeneous course of illness, there may be a sub-group of schizophrenia patients with typically increased rather than attenuated cortisol responses who may have higher social functioning, which may also be in association with basal oxytocin levels and social support.

As far as is known, Rosenfeld et al. (2011) were the first to propose an integrative model to understand how social performance is brought together by biological factors such as dopamine and oxytocin, and cognitive factors such as social cognition in schizophrenia(Rosenfeld et al., 2011). Similar to the previous schizophrenia models, they also emphasized the indispensable role of the dopaminergic system in explaining core deficits in schizophrenia. They proposed an interdependent relationship between the brain correlates of social cognition and social behavior, oxytocin, cortisol and dopamine to explain social impairments and emotional disturbances in schizophrenia. In brief, Rosenfeld et al concluded that while the core features of schizophrenia rely heavily on dysfunctions in the dopaminergic circuits, the network activity involved in fine-tuning of social behavior, which is centrally controlled by the amygdala and oxytocin, could further impact on the social impairments in schizophrenia. Specifically, they hypothesized that the impairments in the dopaminergic
reward systems, the amygdala and oxytocin engender a neural milieu that improperly assigns emotional salience to environmental stimuli and hence causes misinterpretations that result in inappropriate social approach and avoidance responses (Rosenfeld et al. 2011).

Given of this, it is plausible to suppose that impairment in any step of Rosenfeld’s model could ultimately result with social dysfunction. Notably, the Rosenfeld model should not be considered as an alternative explanation for the etiopathogenesis of schizophrenia. It is more of an alternative viewpoint to explain the behavioral findings in schizophrenia and hence may help us to develop future treatment strategies to improve social functioning, which would possibly show high sensitivity yet low specificity in patients with schizophrenia.

1.6. Aims of the thesis

A growing body of literature is now studying the role of the aforementioned domains on social functioning in schizophrenia separately. However, there is a demand for research to construct a bridge between these domains and evaluate their unifying role in giving a form to the social functioning in schizophrenia. Therefore, several studies were conducted in this thesis to shed light on the overlapping features of these domains and study their implications on social functioning in schizophrenia.

More specifically, the aims of the present thesis are (1) to study the effects of metacognition on social cognition, learning and social functioning, (2) to investigate the role of plasma oxytocin levels on cortisol reactivity to stress and particularly explore their relationship with metacognition and social functioning, and lastly (3) to evaluate the predictive role of basal oxytocin levels over the improvement of different domains of social cognition after a specific social cognition training program in a group of schizophrenia patients.

The hypotheses are: (1) There is a certain link between theory of mind abilities and metacognition. (2) Metacognitive skills are able to predict learning and social functioning in schizophrenia. (3) By following the Rosenfeld et al. (2011) model, cortisol reactivity to social stress in schizophrenia might be predicted by endogenous oxytocin, and this neurobiological fine-tuning system is in association with social isolation and may explain social functioning. (4) Lastly, the effect of oxytocin on improvements in social cognition is domain specific. Considering the Rosenfeld model of schizophrenia and the ongoing literature on the specific effects of oxytocin, this effect might be specific to the emotional processing in schizophrenia.
3 main studies were conducted to gather a multi-dimensional database at the end. Accordingly, the first study was designed to answer the first two hypotheses, the second study was proposed to respond to the third hypothesis, and the last study was designed to answer the fourth hypothesis of this thesis.
CHAPTER 2

Study 1 - Interconnections between metacognition, theory of mind, motivation, learning potential and their implications on social functioning in schizophrenia

The present study sought to examine the relationship between intelligence, motivation, metacognition, and learning during an experimental cognitive remediation training. It has been hypothesized that metacognition and intrinsic motivation would independently predict learning potential and explain some sub-domains of social functioning. Notably, some parts of this study have been published in the Journal of Psychiatric Disorder (Tas et al., 2012a).

2.1. Materials and methods

2.1.1. Participants

Fifty-two clinically stable patients with schizophrenia were recruited for this study. The patients met DSM-IV criteria for schizophrenia as determined by medical records and confirmed with the Structured Clinical Interview for DSM-IV – Patient Edition (SCID; First et al., 1996). Only patients meeting the criteria of being in remission according to the Schizophrenia Working Group (Andreasen et al., 2005) were included. Of the thirty-two patients meeting the criteria for remission two patients refused participation. Thus, data from thirty patients (53 percent men) were completed. The patients’ mean age was 32.93±12.35 years; the number of years of education was 11.50±2.34, the mean duration of illness was 12.07±10.55 years, and the number of hospital stays was 2±2. All patients received second-generation antipsychotic medication. Chlorpromazine equivalent dosages (CPZ) were calculated for all patients in order to control for the medication effects (Rijcken et al., 2003). Accordingly, mean dosages were 416.25±220.99 mg per day. All patients provided written informed consent and all procedures met institutional ethical board approval.

2.1.2. Procedures

2.1.2.1. Definition of criteria for symptomatic remission
According to the criteria (Andreasen et al., 2005), symptomatic remission has been attained if the following PANSS items are rated as being moderate, mild, minimal or absent (i.e. PANSS score for each item ≤ 3): delusions (PANSS-P1), unusual thought content (PANSS-G9), hallucinatory behavior (PANSS-P3), conceptual disorganization (PANSS-P2), mannerisms (PANSS-G5), blunted affect (PANSS-N1), social withdrawal (PANSS-N4) and lack of spontaneity (PANSS-N5)

2.1.2.2. Clinical and neuropsychological measures

2.1.2.2.1. Symptomatology

The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was used to assess the severity of psychotic positive and negative symptoms. The PANSS is a 30-item semi-structured interview that assesses five symptom categories specifically associated with psychosis, namely, positive symptoms (i.e., hallucinations and delusions), negative symptoms (i.e., avolition and anhedonia), cognitive symptoms (i.e., thought disorder), hostility, and depression. A score from 1 to 7 was assigned to each symptom item, with higher scores indicating more severe psychopathology. The scores for the items within each category are summed to produce a score for each symptom dimension. A clinical psychologist who had received formal PANSS training administered the PANSS.

2.1.2.2.2. Estimated general intelligence

Age-corrected indices of the memory quotient (MQ) were calculated by using the total Wechsler Memory Scale score (WMS-III; Wechsler, 1997). MQs were used as an index for general intelligence as this is a relatively short test that was more appropriate here in terms of the feasibility and the time constraints of the experimental procedure.

2.1.2.3. Metacognition and theory of mind

2.1.2.3.1. The Indiana Psychiatric Illness Interview (IPII)

The IPII (Lysaker et al., 2002) is a semi-structured interview developed to assess how individuals understand their experience with mental illness. A trained psychiatrist conducted the interview, which typically lasted between 30 and 60 minutes. All original procedures from the IPII were followed strictly. The interview is conceptually divided into five sections.
First, rapport is established and participants are asked to tell the story of their lives, beginning with their earliest memory. Secondly, participants are asked if they think they have a mental illness and, if so, whether or not this condition has affected different facets of their life. Thirdly, participants are asked if and how their condition controls their life and, alternately, how they control their condition. Fourthly, they are asked how their condition affects, and is affected by others. Finally, participants are asked about their expectations for the future. The IPII differs from some other psychiatric interviews in that only minimal content is introduced for the participant to comment on and thus results in a self-report that can be analyzed in terms of the metacognitive capacities that appear spontaneously.

2.1.2.3.2. The Metacognition Assessment Scale

The Metacognition Assessment Scale (MAS; Semerari et al., 2003) is a rating scale that assesses metacognitive abilities. It was originally designed to detect growth within psychotherapy transcripts and, in consultation with the authors, has been abbreviated and adapted for the study of IPII transcripts (Lysaker et al., 2005). The MAS differs from other more structured assessments of metacognition in that it focuses on metacognitive functions that arise spontaneously rather than cued, as in a task or referenced in a questionnaire. The MAS contains four scales: ―Understanding of one's own mind‖, or the comprehension of one's own mental states; ―Understanding of others' minds‖, or the comprehension of other individuals' mental states; ―Decentration‖, or the ability to see the world as existing with others having independent motives; and ―Mastery‖, or the ability to work through one's representations and mental states, with a view to implement effective action strategies in order to accomplish cognitive tasks or cope with problematic mental states. The MAS asks the rater to indicate whether the participant has successfully used or failed to use a function for each task. For example, the rater must determine if the participant can identify different emotions they feel and recognize that their understanding of life events is subjective. The full presence of a function is awarded a score of ―1‖, whereas a score of ―0.5‖ is awarded for the partial presence of a function. The highest score obtainable for ―Understanding of one's own mind‖ is ―9‖, for ―Understanding of others' minds‖, an ―8‖, for ―Decentration‖ a ―3‖ and for ―Mastery‖ a ―9‖. There was only one rater and therefore interclass correlation coefficients (ICC’s) were not taken into consideration.
CHAPTER 2 - STUDY 1

2.1.2.3. Theory of Mind

The Hinting Task (Corcoran et al., 1995) is a performance-based test, which consists of ten brief written vignettes, including social hints that the participant is asked to interpret. Total scores range from 0 to 20, with higher scores indicating better performance. The Hinting Task taps into the social-cognitive domain of Theory of Mind (ToM).

2.1.2.4. Motivation assessment

2.1.2.4.1. Intrinsic motivation

Self-reported intrinsic motivation (IM) was measured using an adapted version of the Intrinsic Motivation Inventory (IMI; Plant & Ryan, 1985) for schizophrenia patients (Choi et al., 2010). The IMI-SC consists of 21 items rated on a 7-point likert scale with responses ranging from “not at all true” to “very true”. It is designed to assess a schizophrenia patients’ subjective experience of an activity specifically in an experimental setting. The instrument has five subscales: (1) perceived interest and enjoyment due to task (interest/enjoyment), (2) perceived value and usefulness of the task for the proposed test (value/usefulness), (3) efforts given to accomplish the task (effort), (4) perceived pressure and tension while performing the task (pressure/tension), and (5) perceived autonomy to perform the task (choice). Higher scores indicate a greater IM for performing the task. The scale is highly associated with constructs of motivation for health-related behaviors, including perceived competency for attempting challenging tasks and autonomous treatment engagement (Choi et al., 2010). In the present study, the IMI-SC was conducted after the cognitive remediation training of WCST skills.

2.1.2.4.2 Extrinsic motivation

Perceived need for extrinsic motivation was evaluated with one item (“I believe that, if you have given me a present, some amount of money or something different that I would like to have; I would have performed better”) rated with the same 7-point likert scale used for assessing IM.

2.1.2.5. Perceived competency

The Perceived Competency Scale (PCS; Williams and Deci, 1998) consists of 4 items rated also on a 7-point Likert scale with responses ranging from “not at all true” to “very
true” (e.g., I feel confident in my ability to learn the computer program; I am able to achieve my goals in this program), with higher scores indicative of greater feelings of self-competency for the task. Previous studies suggest that perception of self-efficacy is a central construct of IM and an indirect indicator of internalized motivation (Williams and Deci, 1996). Choi et al (2010) were the first to use the PCS in a similar experimental setting to measure participants’ subjective perception of completing and mastering the learning exercises.

2.1.2.6. Social functioning

The Social Functioning Scale (SFS; Birchwood et al., 1990) measures social functioning, including social engagement/withdrawal (e.g., “how often will you start a conversation at home?”); interpersonal communication (e.g., “how easy or difficult do you find talking to people at present?”); independence/performance (e.g., “how often do you prepare and cook a meal?”); recreation (e.g., “how often do you play a sport?”); prosocial activities (e.g., “how often do you visit friends?”); independence/competence (e.g., “how able are you to budget?”); and employment/occupation (e.g., “when were you last employed?”). The interviewer completed this 79-item questionnaire. Items were rated on a 4-point scale of frequency or ability, with higher scores indicating greater competency.

2.1.2.7. Learning potential (LP) assessment

The WCST is a neuropsychological test sensitive to impairments in executive function. Participants sort cards that vary according to an unspecified matching rule that changes periodically. The current study utilized the number of correct responses meaning the right matching rule between color, shape and number of the card presented as a goal of learning.

Participants received a 128-card computer version of the Wisconsin Card Sorting Task (WCST; Heaton, 1981) with standard instructions at baseline. Eight weeks later, a previously defined structured training procedure, based on cognitive remediation using errorless learning techniques, was administered as training with computer (for details, see Kern et al., 1996). In summary, the training procedures for the WCST used the techniques of errorless learning. The WCST was chunked into its small components to create a hierarchy of to-be-learned skills. The training was held in three steps: stimulus feature identification, card matching, single shift execution, double shift execution. A subject who repeatedly gave the
correct answer for 10 trials in each phase was considered to have successfully completed the task. None of the subjects failed to complete the training. Each phase of training consisted of a series of trials that included self- and other-delivered cues, as well as modeling, explicit instruction, and response feedback to facilitate correct responding and to reduce the possibility of errors. A psychiatrist who received certified training in applying cognitive remediation (C.T.) conducted training. Training typically lasted 30 to 45 minutes. The training material was prepared using PowerPoint for Windows and a freely available psychological experiment tool (PsychoPy 1.71, Nottingham University, UK). After the training period, within the same session, post-training data was collected using the exact same procedure used at baseline.

2.1.2.8. Data analysis

Data was evaluated for normality and in no case was there evidence that variables included in the study violated the assumptions underlying the use of parametric statistical procedures. Pearson correlations were calculated among the outcome parameters for exploring the relationship between variables and identifying multicollinearity. To define LP, we firstly conducted a categorical approach, in which patients were categorized as “non-learners”, “learners” and “high achievers” according to a previously established algorithm (for details, see Schottke et al., 1993). For every pretest score, a test score on a hypothetical parallel test was predicted in a linear regression model and compared with the real post-test score. We categorized a non-learner as one whose post-test score was below the predicted confidence interval. Participants whose scores were 1.5 standard deviations above the group mean gain difference were classified as “high achievers”, whereas the remaining group of patients (who scored in-between) was considered as “learners”. Furthermore, to control for ceiling effects participants whose pre-training number of correct responses was above 86 were also classified as high achievers (Wiedl, 1999), a procedure that has been used in a similar fashion in previous studies of LP (Fiszdon et al., 2006; Rempfer et al., 2006). A between group ANOVA was conducted to identify the differences in IQ, motivation, metacognition and social functioning between learning group categories.

A hierarchical regression model was performed to identify the unique contribution of each variable in predicting the WCST number of correct responses (dependent variable) after training. A hypothetical model was constructed according to the ongoing literature on motivation and metacognition and learning (Choi and Medalia, 2010; Lysaker et al., 2008).
To control for the effects of pretest performance and intelligence, we included the baseline number of correct responses in the WCST in the first step of the regression analysis, and added the estimated intelligence (MQ) score in the second step. The aim of this regression analysis was to observe the unique influence of intrinsic motivation and metacognition on learning from training (i.e. LP) when controlling for differences in baseline performance and intelligence.

Lastly, a series of Pearson correlation analysis were performed to identify the predictors of social functioning subdomains. The parameters, which were correlated social functioning, were considered as potential predictors. All analyses were conducted by commercially available data analyses software (SPSS 20). P values smaller than 0.05 were accepted as significant.

2.2. Results

2.2.1. Data quality

Preliminary analyses were conducted to ensure that there was no violation of the assumptions of normality, linearity, and homogeneity of variances, homogeneity of regression slopes and reliability.

2.2.2. Correlational analyses

The correlations between intelligence, perceived competency, theory of mind, need for extrinsic motivation and subscales of motivation and metacognition are summarized in Table 1. Accordingly, intelligence is found to be related to mastery levels of metacognition (r=.50), but not with intrinsic motivation. Perceived value and usefulness of the training was related to the Hinting Task (r=.44), and metacognitive skills such as self-reflectivity (r=.37), understanding other minds (r=.39), decentration (r=.46) and mastery (r=.46). Need for extrinsic motivation was negatively associated with perception of personal choice to perform the training, the Hinting Task (r=-.47) and with self-reflectivity (r=-.54) and understanding of other minds (r=-.59) subdomains of metacognition. Hinting task was correlated with self-reflectivity and mastery levels of metacognition. In general, metacognitive abilities measured with the MAS were highly inter-correlated whereas intrinsic motivation subscales measured with IMI-SC were found to be less related with each other. Accordingly, interest and enjoyment was correlated only with perceived usefulness and subjective value of the training, but not with perceived effort, autonomy and pressure to complete the training. Lastly,
perceived competency was positively correlated with all subdomains of metacognition, intelligence, ToM skills, value/usefulness and interest/enjoyment subdomains of IM.

Table 2.1: Inter correlations among the variables.

<table>
<thead>
<tr>
<th>Task</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. MQ</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Interest / Enjoyment</td>
<td>.21</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Value / Usefulness</td>
<td>.34</td>
<td>.78**</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Effort</td>
<td>-.03</td>
<td>.32</td>
<td>.38*</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Pressure/ Tension</td>
<td>.29</td>
<td>.07</td>
<td>.11</td>
<td>-.07</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Choice</td>
<td>.13</td>
<td>.27</td>
<td>.19</td>
<td>.38*</td>
<td>.03</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Need for Extrinsic motivation</td>
<td>-.23</td>
<td>-.17</td>
<td>-.18</td>
<td>-.21</td>
<td>.20</td>
<td>-.56**</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Perceived Competency</td>
<td>.38*</td>
<td>.60**</td>
<td>.58**</td>
<td>.09</td>
<td>.03</td>
<td>-.02</td>
<td>-.22</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Hinting Task</td>
<td>.35</td>
<td>.36*</td>
<td>.44*</td>
<td>.05</td>
<td>-.17</td>
<td>.15</td>
<td>-.47**</td>
<td>.53**</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. MC-Self-reflectivity</td>
<td>.27</td>
<td>.29</td>
<td>.37*</td>
<td>.32</td>
<td>.03</td>
<td>.14</td>
<td>-.54**</td>
<td>.65**</td>
<td>.42*</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. MC- Understanding others mind</td>
<td>.25</td>
<td>.26</td>
<td>.39*</td>
<td>.49**</td>
<td>.05</td>
<td>.33</td>
<td>-.59**</td>
<td>.57**</td>
<td>.30</td>
<td>.85**</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. MC- Decentration</td>
<td>.31</td>
<td>.29</td>
<td>.46*</td>
<td>.45*</td>
<td>.10</td>
<td>.10</td>
<td>-.31</td>
<td>.49**</td>
<td>.29</td>
<td>.86**</td>
<td>.74**</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>13. MC- Mastery</td>
<td>.50**</td>
<td>.28</td>
<td>.46*</td>
<td>.23</td>
<td>.27</td>
<td>.03</td>
<td>-.35</td>
<td>.53**</td>
<td>.39*</td>
<td>.81**</td>
<td>.73**</td>
<td>.79**</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: Correlation values in italic type remained significant after multiple correlational analyses.

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).
2.2.3 Between-group ANOVA

Table 2.2 summarizes the between group ANOVA results comparing estimated intelligence, intrinsic motivation and metacognition between non-leaners, learners and high achievers. No differences between learning categories were found in terms of medication (CPZ equivalents \(F(2,27= 1.701, p=0.202\)). Significant group differences were found between high achievers and non-leaners on all factors. In addition to this, there were significant group differences between learners and non-leaners for the memory quotient, the perceived usefulness/value and effort subscales of the IMI, understanding others mind, decentration and mastery levels of metacognition. Finally, differences in self-reflectivity between non-leaners and learners approached statistical significance (\(p=0.061\)).

**Table 2.2**: ANOVA between-group analysis of learning categories

<table>
<thead>
<tr>
<th></th>
<th>non-learners(n:6)</th>
<th>learners(n:14)</th>
<th>high achievers(n:10)</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>MQ</td>
<td>Mean 71.83</td>
<td>S.D. 15.03</td>
<td>Mean 90.00</td>
<td>15.11</td>
<td>Mean 89.40</td>
</tr>
<tr>
<td>Need for Extrinsic motivation</td>
<td>6.86</td>
<td>.38</td>
<td>4.85</td>
<td>5.60</td>
<td>6.72</td>
</tr>
<tr>
<td>IMI-SC Interest / Enjoyment</td>
<td>32.67</td>
<td>9.00</td>
<td>36.93</td>
<td>7.00</td>
<td>42.50</td>
</tr>
<tr>
<td>IMI-SC Value / Usefulness</td>
<td>30.17</td>
<td>10.89</td>
<td>41.00</td>
<td>9.07</td>
<td>42.70</td>
</tr>
<tr>
<td>IMI-SC Effort</td>
<td>18.33</td>
<td>2.50</td>
<td>25.57</td>
<td>5.47</td>
<td>22.60</td>
</tr>
<tr>
<td>IMI-SC Pressure/ Tension</td>
<td>20.83</td>
<td>5.34</td>
<td>19.07</td>
<td>7.05</td>
<td>19.40</td>
</tr>
<tr>
<td>IMI-SC Choice</td>
<td>24.00</td>
<td>8.72</td>
<td>32.64</td>
<td>7.61</td>
<td>27.70</td>
</tr>
<tr>
<td>Hinting Task</td>
<td>10.71</td>
<td>3.73</td>
<td>13.71</td>
<td>2.64</td>
<td>13.20</td>
</tr>
<tr>
<td>MC-Self-reflectivity</td>
<td>3.17</td>
<td>1.03</td>
<td>5.32</td>
<td>2.24</td>
<td>6.25</td>
</tr>
<tr>
<td>MC-Understanding other minds</td>
<td>2.92</td>
<td>0.38</td>
<td>4.43</td>
<td>1.14</td>
<td>4.65</td>
</tr>
<tr>
<td>MC-Decentration</td>
<td>0.50</td>
<td>0.55</td>
<td>1.57</td>
<td>0.92</td>
<td>1.85</td>
</tr>
<tr>
<td>MC-Mastery</td>
<td>3.50</td>
<td>1.05</td>
<td>5.68</td>
<td>1.91</td>
<td>6.50</td>
</tr>
</tbody>
</table>
Note: MQ: Memory quotient, IMI-SC: Intrinsic Motivation Inventory for Schizophrenia. MC: Metacognition

2.2.4 Multiple regression analyses

2.2.4.1. Predictors of learning potential

Before the hierarchical regression model was performed, to ensure no violation of multicollinearity, it has been decided to include the total IMI score instead of subscale scores and mastery levels of metacognition into the equation. Variance inflation factors were checked before the analyses. The results of regression model including the pre-training WCST number of correct responses (Step 1), MQ (Step 2), total IMI (Step 3) and metacognitive mastery (Step 4) are presented in Table 2.3. In the last step, metacognitive mastery was included, firstly because metacognitive mastery has specifically been found as a potential mediator social functioning in previous studies (Lysaker et al., 2008), and secondly due to the models of development of intrinsic motivation and learning (Ryan and Deci, 2000; Flavell, 1979). Accordingly, pre-training performance was entered in the first step, and significantly explained 22.5% of the variance. Including memory quotient scores in the model showed that it explained a further 6.5% of the variance, with intrinsic motivation accounting for another 8.5%, though non-significantly. Metacognitive mastery was found as the only variable that significantly explained 48% of the overall variance in the last step. Previous performance and metacognitive mastery uniquely predicted the post-training performance when variance from other variables was controlled for. The memory quotient and total intrinsic motivation failed to explain overall variance independently in any of the steps, although they seem to have a contributing role in the equation.
Table 2.3: Hierarchical regression analysis for predicting learning potential

<table>
<thead>
<tr>
<th>Step</th>
<th>B</th>
<th>t value</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>Baseline WCST number of correct responses</td>
<td>.70</td>
<td>2.85</td>
</tr>
<tr>
<td>Step 2</td>
<td>Baseline WCST number of correct responses</td>
<td>.66</td>
<td>2.70</td>
</tr>
<tr>
<td></td>
<td>MQ</td>
<td>.47</td>
<td>1.57</td>
</tr>
<tr>
<td>Step 3</td>
<td>Baseline WCST number of correct responses</td>
<td>.66</td>
<td>2.83</td>
</tr>
<tr>
<td></td>
<td>MQ</td>
<td>.33</td>
<td>1.09</td>
</tr>
<tr>
<td></td>
<td>IMI-SC Total score</td>
<td>.31</td>
<td>1.87</td>
</tr>
<tr>
<td>Step 4</td>
<td>Baseline WCST number of correct responses</td>
<td>.50</td>
<td>2.16</td>
</tr>
<tr>
<td></td>
<td>MQ</td>
<td>.07</td>
<td>.24</td>
</tr>
<tr>
<td></td>
<td>IMI-SC Total score</td>
<td>.19</td>
<td>1.20</td>
</tr>
<tr>
<td></td>
<td>Mastery – Metacognition</td>
<td>5.31</td>
<td>2.23</td>
</tr>
</tbody>
</table>

**Step 1:** $R^2 = .225$, df=1, 28, p=.008;  
**Step 2:** $R^2 = .290$, df=1, 27, p=.010; Sig. F Change: p=.079  
**Step 3:** $R^2 = .375$, df=1, 26, p=.006; Sig. F Change: p=.088  
**Step 4:** $R^2 = .479$, df=1, 25, p=.002; Sig. F Change: p=.042

**Note:** Dependent Variable: Post training WCST number of correct responses. MQ: Memory quotient. IMI-SC Total score: Intrinsic Motivation Inventory for Schizophrenia Total score.

**2.2.4.2. Predictors of social functioning**

The results of the inter-correlations among the predictors and subscales of social functioning were summarized in table 2.4. Accordingly, we noted that hinting task was correlated with interpersonal relationships, independence, competence and performance subscales of SFS. Notably, the perceived efforts to complete the cognitive remediation training were in relation with occupational functioning subscale of SFS. Equally interesting, significant correlations emerged between the metacognitive decenteration, the independence/competence and performance subscales of social functioning. Besides, metacognitive self-reflectivity was in significant association with occupational functioning and independence competence subscales of social functioning. Lastly, as a note of caution, a summary of the main findings of this study was presented in Chapter 5.
Table 2.4: Pearson correlation analyses among the independent predictors and social functioning subdomains

<table>
<thead>
<tr>
<th></th>
<th>SFS-SWI</th>
<th>SFS-IPL</th>
<th>SFS-PSA</th>
<th>SFS-RC</th>
<th>SFS-IND/CP</th>
<th>SFS-IND/PER</th>
<th>SFS-OCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for Extrinsic</td>
<td>-.25</td>
<td>-.29</td>
<td>-.19</td>
<td>-.28</td>
<td>.007</td>
<td>-.09</td>
<td>-.23</td>
</tr>
<tr>
<td>motivation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived competency</td>
<td>-.024</td>
<td>.19</td>
<td>.28</td>
<td>.02</td>
<td>.38*</td>
<td>.28</td>
<td>.35</td>
</tr>
<tr>
<td>IMI interest /</td>
<td>-.11</td>
<td>-.001</td>
<td>.05</td>
<td>.08</td>
<td>-.03</td>
<td>.12</td>
<td>.06</td>
</tr>
<tr>
<td>Enjoyment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMI Value /</td>
<td>-.06</td>
<td>.18</td>
<td>.25</td>
<td>.19</td>
<td>.23</td>
<td>.36</td>
<td>.16</td>
</tr>
<tr>
<td>Usefulness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMI Effort</td>
<td>-.06</td>
<td>.21</td>
<td>-.07</td>
<td>.03</td>
<td>.05</td>
<td>.09</td>
<td>.39*</td>
</tr>
<tr>
<td>IMI Pressure/</td>
<td>-.31</td>
<td>-.14</td>
<td>.10</td>
<td>-.26</td>
<td>.007</td>
<td>-.12</td>
<td>.14</td>
</tr>
<tr>
<td>Tension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IMI Choice</td>
<td>.13</td>
<td>.13</td>
<td>.15</td>
<td>.09</td>
<td>-.29</td>
<td>.03</td>
<td>-.03</td>
</tr>
<tr>
<td>Hinting Task</td>
<td>.32</td>
<td><strong>.57</strong></td>
<td>.25</td>
<td>.37</td>
<td><strong>.49</strong></td>
<td><strong>.41</strong></td>
<td>.24</td>
</tr>
<tr>
<td>MC-Self reflectivity</td>
<td>.14</td>
<td>.36</td>
<td>.19</td>
<td>.22</td>
<td><strong>.39</strong></td>
<td>.27</td>
<td><strong>.45</strong></td>
</tr>
<tr>
<td>MC-Understanding others</td>
<td>.001</td>
<td>.17</td>
<td>.18</td>
<td>.12</td>
<td>.31</td>
<td>.16</td>
<td>.27</td>
</tr>
<tr>
<td>mind</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MC-Decentration</td>
<td>.14</td>
<td>.35</td>
<td>.31</td>
<td>.35</td>
<td><strong>.42</strong></td>
<td><strong>.43</strong></td>
<td>.26</td>
</tr>
<tr>
<td>MC-Mastery</td>
<td>-.04</td>
<td>.19</td>
<td>.14</td>
<td>.07</td>
<td>.33</td>
<td>.10</td>
<td>.27</td>
</tr>
</tbody>
</table>


*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

2.3. Interim Discussion

Learning in schizophrenia has been an important topic of interest, which is particularly relevant for cognitive remediation and rehabilitation research carried out in recent years. Nevertheless, little research has convincingly revealed the motives that facilitate
learning in schizophrenia patients. To our knowledge, this is the first study focusing on learning through the lens of metacognition and motivation, and their implication on social functioning in patients with symptomatically remitted schizophrenia. Metacognitive deficits in schizophrenia have recently been related to a large number of diverse processes that can malfunction in a number of different ways (Bacon and Izaute, 2009; Brüne et al., 2008; Lysaker et al., 2011a). Accordingly, the results of Study 1 suggest that impairments in metacognition are associated with social functioning, learning potential and motivation, and are independent from symptom severity in schizophrenia. One of the first works on metacognition in schizophrenia was carried out by Baker and Morrison (1998), who found that the patients’ lack of metacognitive awareness predicted the experience of auditory hallucinations. Following this work, a thought-provoking study evaluated the neuropsychological basis of insight in a group of first episode schizophrenia patients (Koren et al., 2004). They designed a metacognitive version of the WCST, which consisted of the standard administration of the WCST followed by the rate of patient’s level of confidence to their responses for the correctness of each sort. The patients were also asked if they would like their answer to be “counted” towards their overall performance. In brief, Koren and his colleagues found that patients who had better insight to their illness also showed higher performance in this novel free-choice metacognitive version of the WCST. Following this study, Lysaker et al. (2005) presented their first results on the role of metacognition in neurocognition, symptoms, insight, and quality of life. They recruited 61 men with schizophrenia and found that understanding one’s own mind (self-reflectivity) was linked to better neurocognition and lesser emotional withdrawal. They further demonstrated that greater metacognition skills in the context of successful problem solving (metacognitive mastery) were associated with verbal memory and insight. Recent studies highlighted the role of metacognition in social functioning. For instance, metacognitive self-reflectivity in schizophrenia was found to be related to occupational functioning in a longitudinal study (Lysaker et al., 2010). The same research group further demonstrated that social functioning in schizophrenia is mediated by mastery, a domain of metacognition that represents a metacognitive capacity to form integrated narratives built around complex and coherent accounts of how the mental states of both oneself and others change over time, and then to use this kind of mentalistic information for purposeful problem solving (Lysaker et al., 2010c; Tas et al., 2012). Hence, they recruited 102 adults with schizophrenia and screened administered the MAS and self-report measures of social functioning. Using structural equation modeling, metacognitive mastery was found to mediate the frequency of social
contact and capacity for social relatedness even when negative and cognitive symptoms were accounted for. The promising effects of metacognitive mastery were also demonstrated by utilizing performance-based measures of social functioning (Lysaker et al., 2011b).

The present study replicated the promising effects of metacognition on social functioning, because it shows that self-reflectivity and decentration subdomains of metacognition were related to occupational functioning and the patients’ perceived competence and independence to successfully accomplish the tasks in their own social environment. However, specific effects of metacognitive mastery on social functioning were not found. Our explanation for this negative result is that our sample consisted of symptomatically remitted patients who were already adequately able to cope with their social problems as indicated by higher metacognitive mastery scores in the MAS, as compared to the previous studies. Thus, this ceiling effect may have masked the possible associations between metacognitive mastery and social functioning in our data. Nevertheless, metacognitive mastery stayed as an independent predictor of learning potential even when motivation and neurocognition were controlled for in our hierarchical regression analyses in Study 1.

To date, there is some evidence suggesting that discrete social cognitive capacities are different from synthetic metacognitive skills. Although they appear to work in conjunction, they also have non-overlapping parts. For instance, studies on attributional style, which in theory requires successful emotion perception and theory of mind capacities, did not show significant correlations with these domains although they all had separate correlations with symptom severity and functioning (Baker et al., 1998; Humphreys et al., 2006). Recently, Lysaker et al. (2013) hypothesized that discrete social cognitive capacities are different from synthetic metacognitive ones (Lysaker et al., 2013). They conducted a principal component analysis with the data collected from 95 individuals with schizophrenia in which hinting task, reading the mind in the eyes test and Bell-Lysaker emotion recognition tests were used as measures of social cognition, and MAS was conducted as a measure of metacognition. They found that social cognition and metacognition were grouped under distinct factors and correlated with different outcome variables, where social cognition was linked with negative symptoms, poorer education and poorer intellectual function, whereas metacognition was associated with disorganization symptoms, frequency of social contacts and the capacity for relatedness and flexibility in abstract thoughts. Notably, theory of mind skills showed moderate associations with self-reflectivity and mastery but not with decentration and
understanding others’ mind subdomains of metacognition in Study 1. Moreover, theory of mind capacity as measured with the hinting task was associated with interpersonal relations, social performance and social independence subdomains of social functioning. Despite these correlations between theory of mind and metacognition in Study 1, intrinsic motivation was only in association with metacognition but not with ToM skills. Notably, this negative result indirectly supports the distinct features of ToM and metacognition described in the Lysaker et al. (2013) study. In fact, Flavell and Miller (1993) pointed out that understanding the sources of knowledge and the nature of representations (ToM) provides a foundation for later metacognitive knowledge and is a prerequisite to think about how the engendered information should be organized to reach a social conclusion that is unique for each individual. In other words, the results of Study 1 supported the proposal that theory of mind deficits in schizophrenia impact on metacognition. However, the construction of theories to predict ours and others mental states, and updating these theories as new findings shows the older ones to be inadequate, which may not be merely a product of theory of mind.

Despite the well-replicated findings on the associations between metacognition and functional outcome, little is known about the way metacognition acts on functioning and the patients’ individual potential to benefit from environmental stimuli or cognitive tasks. Nevertheless, some recent studies propose a link between the therapy outcome and metacognitive skills of schizophrenia patients. For instance, metacognitive mastery was measured in 62 adults with schizophrenia or schizoaffective disorder enrolled in a 6-month program of psychosocial interventions (Davis et al., 2011). After treating the data with the categorical approach, researchers found that patients with higher metacognitive mastery also had stronger therapeutic compliance. Furthermore, Moritz et al. (2007) developed a metacognitive training program for schizophrenia patients. They demonstrated the favorable effects of training on social functioning, symptom severity and attributional bias (reviewed in Moritz et al., 2010). Here, Study 1 demonstrated that although metacognition may have a direct influence on social functioning, differently from the former well-studied domains in schizophrenia, it may have potential to affect other factors that are akin to real life. It may be that motivation and self-competency were associated with metacognition in that extent.

The putative role of motivation and perceived competency in performing a task has recently been studied in schizophrenia (Choi et al., 2010a). Researchers have found significant correlations between self-competency and all subdomains of IMI. The highest
correlation coefficients were observed in the personal interest and enjoyment subdomains of IMI, which was the same as in Study 1. Besides this, in another study of the same research group (Choi et al., 2010b), it was shown that baseline perception of self-competency is an independent predictor of learning performance, even when variance for baseline arithmetic ability, attention, motivation, and feelings of treatment autonomy were statistically controlled for. Choi et al. concluded that akin to healthy individuals, patients with schizophrenia should also believe that their actions are capable of producing a favorable outcome, which is indeed the definition of self-competency. However, Choi et al. (2010c) treated self-competency as an independent domain in their studies and suggested the use of therapeutic techniques that would ultimately affect motivation and self-competency. However, according to the results of Study 1, self-competency appears to be a product of metacognition, theory of mind and intelligence in schizophrenia. In sum, with the results of Study 1, it appears to be that an individual’s perception of competency is a sophisticated act of thinking that is linked with theory of mind, intelligence and metacognition in schizophrenia.

Before social neuroscience and the study of social cognition began to contribute to research on schizophrenia, the small effect sizes found in psychosocial interventions were attributed mostly to individual neurocognitive incapability, which evidently has a negative impact on the potential to benefit from training and practice, which was specifically referred to here as learning potential (LP) (Wykes et al., 2008). However, there are other factors that hamper the success of therapeutic interventions in schizophrenia such as an individuals’ motivation to benefit from training. Motivational deficits in schizophrenia have always been considered a part of the negative symptoms (Barch, 2005), although recent studies have defined motivational deficits as being an independent predictor of social functioning (Nakagami et al., 2008; 2010). Motivation has been defined as an “internal state, need, or desire that serves to incite, direct, and maintain goal-oriented behaviors and is believed to be implicated in all learned responses and can either foster or hinder future actions” (Kleinginna and Kleinginna, 1981). In line with this definition, it is plausible to suggest that motivational deficits can predict some variance in learning a specific task, which has recently been shown in a regression model in schizophrenia (Choi et al., 2010c). As a result of these previous findings, recent cognitive remediation strategies have already started to use paradigms that attempt to induce intrinsic motivation (Medalia et al., 2011).
As mentioned in the introduction, studies on motivation and schizophrenia have highlighted the self-determination theory (SDT) by Deci and Ryan (1985) as a possible way to model motivational deficits (Medalia and Saperstein, 2011). The SDT proposes a two-sided model where intrinsic motivation arising from intrinsic regulation is at the top level and motivational up-regulation by extrinsic incentives is at the bottom level (Ryan and Deci, 2000). Notably, these two distinct domains are integrated with each other, through the agency of self-regulation, which reflects the individuals’ capacity for altering behavior (Deci and Ryan, 2000). Notably, people who develop a superior pathway to facilitate intrinsic motivation through self-regulation since childhood may voluntarily participate in life events or social and cognitive tasks more often than those who don’t. Currently, motivational deficits and anhedonia are well known as core and independent symptoms of schizophrenia (Medalia and Saperstein, 2011). Moreover, the psychopharmacological therapies in schizophrenia further contribute negatively to motivational domains through their adverse effects on reward processing and extrapyramidal effects (Artaloytia et al., 2006; Lambert et al., 2004). Hence, facilitating intrinsic motivation through “liking” appears to be an unattainable goal for patients with schizophrenia. Nevertheless, a recent study found that intrinsic motivation deficits in schizophrenia is a dynamic process that changes over time (Nakagami et al., 2010) and actually can be fostered with strategies attempting to improve perceived interest and enjoyment. The same research group also conducted another study in 2008 in which they found intrinsic motivation strongly correlated with social functioning and neurocognition in a large group of schizophrenia patients (Nakagami et al., 2008). They further demonstrated that when intrinsic motivation is modeled as a mediator between cognition and functional outcome the fitness of the model increases to a large extent. Taken together, especially with the unique predicting role of mastery levels of metacognition and correlations in this study (Study 1), it seems that having the ability to think about thinking in both self and environmental processes promotes the understanding of the value and usefulness of a particular task, and hence contributes to higher success related with the task. In light of these findings, stimulating motivation through implementing strategies that have a favorable influence on metacognitive knowledge can be considered as an alternative approach for improving learning and intrinsic motivation for training programs in schizophrenia. Such assumption is also in line with the SDT, which argues that conscious evaluation of a behavioral goal or regulation, such that is perceived as personally important or critical, enhances intrinsic motivation by introjecting this extrinsic motivation and integrating it to the self (Deci et al., 1994; Deci and Ryan, 2000). Lastly, differently from the
previous studies, study 1 also demonstrated positive effects of perceived usefulness and value on social functioning in schizophrenia. Because these subdomains of intrinsic motivation were in close relationship with the individual’s metacognition, it is plausible to argue that metacognition may also indirectly influence social functioning through motivation in schizophrenia.

In addition, concerning the SDT, the results of this study (Study 1) suggest that patients with poor motivation, low levels of metacognitive skills and poor theory of mind are the ones that perhaps need more extrinsic motivation. Several studies of cognitive remediation in schizophrenia use monetary incentives to reduce dropout rates (Horan et al., 2011b). This approach may indeed negatively impact upon the efficacy of the intervention, firstly because including patients who consider extrinsic motivation as prior to intrinsic can result with a group of patients with poorer LP. And secondly, extrinsic incentives may also mask the intrinsic value and subjectively perceived usefulness of the training. This may further explain why such studies report smaller effect sizes of the intervention compared to community care-based studies (Brekke et al., 2009).

Notably, the results of this study suggest the presence of considerable variability in LP of patients with schizophrenia, which arguably interacts with the patients’ motivation and metacognition. Consequently, this interdependence of LP with motivation and metacognition may have substantial implications for the efficacy of cognitive remediation training (CRT) in schizophrenia. Raffard et al. (2009) have highlighted that LP can be used as a tool in predicting treatment outcome after CRT. In sum, the benefit of CRT might be less for patients with poorer LP. Therefore, a pre-treatment assessment of LP, in consideration of IM and metacognition, may be used as a screening tool to recruit patients who are more likely to benefit from CRT. Alternatively, Wykes and Reader (2005) have argued that the transfer from a training task to real-life performance critically depends on improving motivation and metacognition in patients with schizophrenia. This could be achieved either by explicitly teaching metacognitive skills to promote active monitoring of one’s own performance, or by implementing educational techniques such as scaffolding and errorless learning, which may present a clear perception of success and enjoyment.
Study 2- Oxytocin as a predictor of social cognition training: domain specific features.

Recently, family-assisted social cognition and interaction training (F-SCIT) was found to be effective in improving quality of life, social functioning, and social cognition in schizophrenia patients (Tas et al., 2012b). The purpose of this study was to explore the role of basal plasma oxytocin levels to predict treatment response of the schizophrenia patients who received F-SCIT. Specifically, this worked focused on the improvements of social cognition domains that may potentially be predicted by the oxytocinergic system.

3.1. Materials and methods

3.1.1. Participants

Nineteen (11 men) patients with SCID-confirmed DSM-IV diagnosis of schizophrenia were recruited after giving written informed consent. All participants were clinically stable and were outpatients. Exclusion criteria included chronic physical illness, current substance abuse, mental retardation, or acute psychotic episode in the last 6 months. The mean age was 33.32 ±11.57 years and mean years of education were 11.95 ±1.72. Participants’ average duration of illness was 12.63 ±9.99 years with mean lifetime number of psychiatric hospitalizations of 2.63 ± 2.27. Chlorpromazine equivalents were calculated for all patients in order to control for medication effects, and the group mean was 484.38 ± 275.51 (see Table 2.1). Notably, none of the female participants were receiving oral contraception. The study was approved by the local institutional review board. The sociodemographic and clinical variables are summarized in table 3.1.
Table 3.1: Sociodemographic and clinical variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>SD</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>33.32</td>
<td>11.57</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td>11 (%57.89)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td>8 (%42.11)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>11.95</td>
<td>1.72</td>
<td></td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>12.63</td>
<td>9.99</td>
<td></td>
</tr>
<tr>
<td>Number of hospitalization</td>
<td>2.63</td>
<td>2.27</td>
<td></td>
</tr>
<tr>
<td>Last year hospitalization</td>
<td>.32</td>
<td>.58</td>
<td></td>
</tr>
<tr>
<td>CPZ equivalent</td>
<td>484.38</td>
<td>275.51</td>
<td></td>
</tr>
<tr>
<td>PANSS Positive</td>
<td>11.16</td>
<td>3.20</td>
<td></td>
</tr>
<tr>
<td>PANSS Negative</td>
<td>17.21</td>
<td>6.35</td>
<td></td>
</tr>
<tr>
<td>PANSS General</td>
<td>27.58</td>
<td>7.53</td>
<td></td>
</tr>
</tbody>
</table>

Notes: CPZ; Chlorpromazine equivalents. PANSS; Positive and Negative Syndrome Scale

3.1.2. Procedures
3.1.2.1. Intervention

Participants received the F-SCIT training that is an extension of the Social Cognition and Interaction Training (SCIT) developed by Roberts et al. (2006). The SCIT is a structured group intervention for schizophrenia patients targeting dysfunctional social cognitive processes, including emotion perception, theory of mind (ToM), which refers to the capacity to infer one’s own and other persons’ mental states, decision-making, and attributional style. The F-SCIT was designed as a 14-session group training once a week for 80 minutes with a 15-minute break, comprising the same three phases of SCIT. In contrast to the original SCIT version, the number of sessions assigned to each of the three phases was slightly changed as follows: 3 sessions were assigned to “Emotion perception”, 5 sessions to “ToM and attributional style”, and 6 sessions to “Integration and Transfer” (see details Tas et al., 2012).

3.1.2.2. Social cognitive assessment

Five widely used social cognition tests were conducted before the beginning of the training and within the two weeks after the F-SCIT to evaluate three basic cognitive domains,
namely emotion perception (EP), theory of mind (ToM) skills, and attribution style (AS). The performance tests were administered according to standard instructions by a trained psychiatrist and then evaluated by a different psychiatrist and a psychologist together to improve accuracy and rule out interrater differences.

Specifically, emotion perception was measured using the Face Emotion Identification Task (FEIT) and the Face Emotion Discrimination Task (FEDT; Kerr and Neale, 1993) total number of correct responses to the identification of six basic emotions (happiness, sadness, anger, fear, surprise, and ashamed) over presented faces and to the discrimination of these emotions over two faces presented in the same screen.

Affective components of ToM was evaluated using the Reading-the-Mind-in-the-Eyes Test (RMET; Baron-Cohen et al., 2001), number of correct responses over one of four words describing best what a person of whom the region surrounding the eyes is visible thinks or feels.

Cognitive components of ToM was measured with the Hinting task (Corcoran et al., 1995), and. The Hinting Task which is supposed to measure the social-cognitive domain of the ToM consists of ten brief written vignettes, including social hints that the participant is asked to interpret. Total number of correct responses scores range from 0 to 20, with higher scores indicating better performance. A total score of the test is calculated over the scoring sheet.

Attributional style was measured with The Internal, Personal, and Situational Attributions Questionnaire (IPSAQ) (Kinderman and Bentall, 1996) which has 32 hypothetical social situations, which are read out to subjects. The subjects are expected to make causal attributions. These attributions are classified as internal (related to self) and external (personal or situational). A bias made to internalize negative situations is calculated as the personalization bias (PB) whereas a bias made to externalize negative situations is calculated as the externalization bias (EB).

3.1.3. Blood sample collection and assessment

Blood samples were collected and through a peripheral venous catheter only at pre-training (baseline).

3.1.3.1. Plasma oxytocin assessment

To measure basal oxytocin levels, another five cubic centimeters of blood were collected before the beginning of the experiment to EDTA tubes containing the polypeptide
aprotinin (EDTA-Aprotinin Tubes, Greiner Bio-One GmbH, Germany) and centrifuged at 4°C at 4000g for 20 min after which plasma was separated into two tubes. Plasma was stored in a freezer at -80°C until the assessment day and assayed as duplicate. For the analyses, considering the debate on the plasma extraction procedure (Szeto et al., 2011), we preferred to use a novel commercially available extraction-free Elisa kit (Bachem S-1355 Oxytocin - EIA Kit, Extraction-free CE-marked). For human serum or plasma samples, typical sensitivity (Av. IC50) was 0.15 ng/ml with a range of 0-10 ng/ml.

3.1.5. Data Analyses

Four participants did not agree to give blood sample, thus the analyses were completed on fifteen participants who received the F-SCIT. The data was checked for the assumptions of conducting linear statistics in the preliminary step. The effects of F-SCIT on social cognition domains were tested by paired t tests. We conducted bivariate correlations between the predictors of interest (oxytocin levels, IQ and age), pre-treatment scores and the gain scores of outcome factors. Gain scores indicate change with the therapy relative to the baseline and calculated by subtracting pre-treatment scores from the post treatment scores (e.g. Post-training Eyes test – Baseline Eyes test). In addition to bivariate correlations, we also regressed each factor (post-score) on the predictors to take into account, shared variance of the individual predictors. In these multiple regression analyses, the pretreatment score was entered in the first step to control for initial status, such that the result shows prediction of cognitive change between pre- and posttest. To maintain reliable predictive power, we selected only those predictors that are related (p < .10) to the gain scores and entered them in the second step of each model. Age and IQ was also included to this step as previously defined hypothetical confounders of treatment outcome in social cognition trainings (Kurtz and Richardson, 2011). We preferred the backward method to the forward method because of suppressor effects, which occur when a predictor has a significant effect but only when another variable is held constant.

The final models of the multiple linear regression analyses, which are reported later, are the most significant models with the highest F-ratios and the highest adjusted multiple determination coefficients (R² corrected). Specifically, we indicate the variance inflation factor (VIF) for each predictor of the final models. As our regression analyses aimed to build hypotheses, the probability value to remove predictors from the models was left at the SPSS default mode of greater than .10.
3.2. Results

Table 3.2: Mean outcome variables

<table>
<thead>
<tr>
<th></th>
<th>Pre-training</th>
<th>Post-training</th>
<th>Gain score</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Face recognition test</td>
<td>11.47</td>
<td>2.90</td>
<td>14.53</td>
<td>2.17</td>
</tr>
<tr>
<td>Face discrimination test</td>
<td>24.80</td>
<td>2.40</td>
<td>26.87</td>
<td>2.39</td>
</tr>
<tr>
<td>Hinting task</td>
<td>13.20</td>
<td>2.43</td>
<td>15.80</td>
<td>1.90</td>
</tr>
<tr>
<td>Eyes test</td>
<td>20.47</td>
<td>4.39</td>
<td>20.47</td>
<td>4.85</td>
</tr>
<tr>
<td>Externalizing Bias</td>
<td>2.67</td>
<td>4.62</td>
<td>5.07</td>
<td>4.10</td>
</tr>
<tr>
<td>Personalizing Bias</td>
<td>0.64</td>
<td>0.28</td>
<td>0.61</td>
<td>0.20</td>
</tr>
</tbody>
</table>

The mean plasma pre-treatment oxytocin levels were 263.53±166.21 pg/ml. Table 3.2 represents the mean social cognitive outcome variables and their statistical differences. Accordingly, the mind in the eyes test and the personalizing bias score of IPSAQ did not differ after the F-SCIT training. Notably, the gain score for face recognition was in negative significant association with the gain score for personalizing bias (r=-.56; p=.03). Besides, the pre-treatment hinting task performance showed negative correlations with the gain score for the hinting task (r=-.64; p=.011). Regarding the link with oxytocin, neither the pre-treatment social cognition scores, nor the gain scores were correlated with basal oxytocin levels. Nevertheless, an approaching significance emerged for the correlation between face discrimination test gain score and plasma oxytocin levels (p=0.07). The results of the correlation analyses between the gain scores, age, IQ and plasma oxytocin levels are summarized in table 3.3.
Table 3.3: Correlation analyses between the predictors of interest and social cognition gain scores.

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Oxytocin levels</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. IQ</td>
<td>-.19</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Age</td>
<td>-.10</td>
<td>.33</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Face recognition-GS</td>
<td>.24</td>
<td>-.02</td>
<td>.25</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Face discrimination-GS</td>
<td>.47</td>
<td>-.08</td>
<td>.18</td>
<td>.35</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Hinting Task-GS</td>
<td>-.02</td>
<td>-.39</td>
<td>-.04</td>
<td>.09</td>
<td>.28</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Eyes test-GS</td>
<td>.16</td>
<td>-.13</td>
<td>-.01</td>
<td>-.04</td>
<td>.14</td>
<td>.39</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>8. Externalizing bias-GS</td>
<td>.09</td>
<td>.01</td>
<td>.25</td>
<td>-.08</td>
<td>-.22</td>
<td>.10</td>
<td>-.48</td>
<td>1</td>
</tr>
<tr>
<td>9. Personalizing bias-GS</td>
<td>-.28</td>
<td>.13</td>
<td>-.08</td>
<td>-.56*</td>
<td>-.40</td>
<td>-.26</td>
<td>-.22</td>
<td>.06</td>
</tr>
</tbody>
</table>

Notes: **. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

The summary of the regression analyses is presented in table 3.4. Age and IQ levels of the participants observed as potential predictors of treatment response for social cognition domains, although the only significant model was for hinting task (p=0.043). Most importantly, we found that basal oxytocin levels (Beta=5.254, p= 0.038) independently predicted the face discrimination test outcome with a corrected $R^2$ of .31 and reached almost significance (p=.067) as a whole model with the contribution of IQ (p=.073) and age (p=.747).

Lastly, as a note of caution, a summary of the main findings of this study was presented in Chapter 5.
Table 3.4: Predictors of improvement in social cognition tasks after the training

<table>
<thead>
<tr>
<th>Post Treatment Scores/</th>
<th>Model</th>
<th>Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictors</td>
<td>Analysis</td>
<td>Analysis</td>
</tr>
<tr>
<td></td>
<td>R²</td>
<td>R² corr</td>
</tr>
<tr>
<td>Model 1. Hinting Task</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>.278</td>
<td>.222</td>
</tr>
<tr>
<td>Model 2. Eyes Test</td>
<td>.095</td>
<td>.026</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3. Face recognition</td>
<td>.25</td>
<td>.13</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of illness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4. Face discrimination</td>
<td>.46</td>
<td>.318</td>
</tr>
<tr>
<td>Oxytocin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 5. Externalizing bias</td>
<td>.015</td>
<td>-.061</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 6. Personalizing bias</td>
<td>.313</td>
<td>.199</td>
</tr>
<tr>
<td>IQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: VIF; variance inflation factor; Unstandardized beta values are presented.

3.3. Interim Discussion

Up until now, social cognition and interaction training (SCIT) is one of the most successful structured social cognition training, which involves strategies to enhance emotional perception, theory of mind and attribution style in schizophrenia. The efficacy of the SCIT, particularly in social functioning, occurs through the successful transference of
learned social cognitive skills to daily life and this effect is variable among patients (Tas et al., 2012). Kurtz et al, (2011) conducted an early meta-analysis that explored the social and cognitive moderators of treatment in addition to the effect sizes. In a sample consisting of 692 patients and 19 studies they found that the remediation of social cognitive deficits were effective in all interested domains except for attribution style, social cue perception and positive symptoms. They found that longer duration of illness better predicted the improvements after the training. Interestingly, they demonstrated that younger hospitalized individuals who also received higher antipsychotic medication seemed to benefit more from the training. Notably, the present study explored the substantial influence of improvements in social cognition domains together with their interdependencies and found that improvements on emotion perception were associated with theory of mind skills and attribution style. In addition to that, patients with lower ToM scores had more room to benefit from the training. In regards to age, although not significant, it appears to be that older individuals in this study were more prepared for improvements after the training.

Nowadays, substantial numbers of studies focus on the effects of oxytocin on deficits in schizophrenia. Most recently, we have evidence that oxytocin has a positive influence on emotion perception, empathy, trustworthiness and emotional components of ToM in schizophrenia (reviewed in Feifel, 2012). Accordingly, the effects of oxytocin in a large distribution of behaviors raised a mandatory question, i.e. whether oxytocin directly impacts on these cognitive domains independently or whether fine-tuning effects of oxytocin on the basic levels substantially affect these domains in general. Hence, study 2 was proposed to respond to this question by utilizing the F-SCIT as a social cognition training and evaluating the potential of plasma oxytocin levels to predict improvements on the social cognitive domains after the training. Interestingly, plasma oxytocin levels before the training were only related with the improvement on face discrimination capacities. Considering also the correlations between face discrimination gain scores and other social cognition subdomains, these findings may help us to understand the specific effects of oxytocin on social cognition domains.

Oxytocin impacts also on several social cognitive domains in schizophrenia patients and healthy participants. Although previous factor analyses and studies using model-based statistical approaches successfully identified the inter-independent subdomains of social cognition in terms of the general principles of brain activity, bottom-up processes like emotion perception may generate more top-down cognitive processes like ToM that rely on a
prior bottom-up integration and hence they are hardly dissociable in this perspective. Domes et al. (2007b) recruited 30 subjects, who were shown pictures of eyes of people expressing different feelings. They observed that after oxytocin administration, subjects tended to be more successful in identifying complex feelings, although this was not the case for easy feelings. Equally interesting, several fMRI studies found similar correlations between the amygdala activity and the accurate identification of emotions, which was altered by oxytocin administration (Domes et al., 2007a; Gamer et al., 2010). Human and animal postmortem studies demonstrated that oxytocin receptors in the brain have wide distributions in subcortical regions such as central, anterior, basal, and lateral amygdala, ventromedial hypothalamus, anterior pituitary, suprachiasmatic nucleus, substantia nigra, locus coeruleus, tractus solitaries, reticularis lateralis and nervus vagus (Bao et al., 2008; Dai et al., 1998; Jenkins et al., 1984). Furthermore, ever growing data suggests that oxytocin and vasopressin act as neuromodulators on these subcortical tracts, which in turn impacts on the high cortical areas that are responsible for decision-making, empathy, theory of mind and metacognition (Meyer-Lindenberg and Tost, 2012; Sofroniew, 1980). Considering the correlations between social cognition gain scores and the specific effects of oxytocin on emotion perception in the present study, it is plausible to argue that the effects of oxytocin originate from the bottom processes such as regulating the amygdala activity and synchronizing the emotional salience of the stimuli, as it has been proposed in the Rosenfeld et al model (2010). It should however be noted that plasma oxytocin levels were not directly related with the baseline social cognition measures in the present study.

Nevertheless, the direct effects of oxytocin on emotion perception have been described in some studies in schizophrenia populations. For example, Averbeck et al. (2011) utilized nasal oxytocin in a group of schizophrenia patients and found increased recognition of emotions following the administration (Averbeck et al., 2011). Moreover, Rubin et al. (2011) conducted another study and found that women with schizophrenia who had higher plasma levels of oxytocin identified emotions as being more positive more often than the male schizophrenia patients, although there were no differences in terms of plasma oxytocin levels. Lower plasma oxytocin levels were associated with impairments in the recognition of faces in another study in schizophrenia (Goldman. et al., 2008). The same study demonstrated that these impairments were more pronounced in patients with polydipsic hyponatremia, a disorder, which is characterized by abnormal plasma arginine vasopressin (pAVP) and hypothalamic pituitary adrenal (HPA) response to stress. Lastly, a thought-provoking study
by Walss-Rass (2013) evaluated the effects of plasma oxytocin levels on theory of mind and emotion perception in schizophrenia. Differently from the former studies, they created a performance-based experiment so called the “Waiting room task” to evaluate the social cognitive domains of the patients (Walss-Bass et al., 2013). In brief, the experiment consisted of 26 videos of people who are in a room looking at the camera with direct or indirect gaze yet with different facial expressions. Accuracy of gaze responses is determined objectively by asking the participant, and the accuracy of ToM responses is determined based on normative consensus from previous norming samples. In addition to the capacity scores, self-referential bias scores were also calculated. Accordingly, they found an inverse relationship between plasma oxytocin levels and ToM scores which was under the influence of gaze recognition and perceived emotional salience, which supports the proposal that the high order social cognitive evaluations originate from understanding and perceiving emotional clues.

As mentioned in the introduction, Rosenfeld and his colleagues (2011) were the first who proposed an emotional model in which oxytocin and amygdala activity played a center role to understand social behavior in schizophrenia. It appears to be that the preliminary results of the present study partially support the Rosenfeld model. Rosenfeld (2011) argued that oxytocin may impact on social cognition in two ways. First, oxytocin modulates the emotional salience of the environmental stimuli and hence adjusts the cognitive and behavioral response accordingly. For example, if a social stimulus is appraised as over-threatening, then the attribution of mental states would easily be misinterpreted. Secondly, if an emotional stimulus is appraised as stressful, this would result in the over-activation of the HPA axis and thus may imbalance the social cognitive processes and induce inappropriate approach and avoidance behaviors (Denson et al., 2009; Theodoridou et al., 2013). Notably, if plasma oxytocin has showed potential to predict improvements in emotion perception part of a structured social cognition program, then this result may indirectly support the specific effects of oxytocin on basic emotional processing capacities in schizophrenia.

Taken as a whole, it appears to be that oxytocinergic activity in the brain alters the basic emotional processing streams which substantially impact on high order social cognitive processes. Specifically, although with some limitations, this work identified two potential values that may shape grading decisions: 1) based on the present findings, plasma oxytocin levels may be an important treatment predictor for the emotional perception parts of social cognitive interventions in schizophrenia, and inclusion criteria based on the patients’ basal
plasma oxytocin levels may be of specific interest to the patients with higher basal oxytocin levels; and 2) in comparison with the other social cognition domains, basal oxytocin levels are most related with emotion perception, which indirectly supports the Rosenfeld model.
CHAPTER 4

Study 3-Cortisol response to stress in schizophrenia: the associations with oxytocin, social support and social functioning

Previous studies reported attenuated cortisol reactivity to social stress as one possible explanation for poor social functioning in schizophrenia. Recent research has demonstrated that the glucocorticoid system and the oxytocin are central to stress regulation, and hence, essential for adaptive behavior. This work studied the association between the basal oxytocin levels and stress-induced cortisol levels in schizophrenia, as well as the impact of the cortisol response on social functioning and social isolation.

4.1. Materials and methods

4.1.1. Participants

Thirty-two adult patients (15 men) with SCID-confirmed DSM-IV diagnosis of schizophrenia were recruited after giving informed consent in writing. All participants were recruited from the psychosis Unit of Celal Bayar University Hospital and were clinically stable and were outpatient. Exclusion criteria included chronic physical illness, current substance abuse, mental retardation or acute psychotic episode in the last 6 months and benzodiazepine use as medication. The mean age was 34.07 ±8.53 years and mean years of education were 11.53 ±3.63. Participants’ average duration of illness was 13.00 ±7.03 years with mean lifetime number of psychiatric hospitalizations of 2.35 ± 1.55 (see Table 4.1). Chlorpromazine equivalents were calculated for all patients in order to control for medication effects, and the group mean was 448.43 ± 276.64. Notably, none of the female participants were receiving oral contraception. The study was approved by the local institutional review board.
### Table 4.1: Sociodemographic and clinical variables

<table>
<thead>
<tr>
<th></th>
<th>N/</th>
<th>Mean</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15(46.88%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>17(53.12%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>34.07</td>
<td>8.53</td>
<td></td>
</tr>
<tr>
<td>Education (years)</td>
<td>11.53</td>
<td>3.63</td>
<td></td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>13.00</td>
<td>7.03</td>
<td></td>
</tr>
<tr>
<td>PANSS Positive</td>
<td>12.61</td>
<td>3.66</td>
<td></td>
</tr>
<tr>
<td>PANSS Negative</td>
<td>15.48</td>
<td>5.61</td>
<td></td>
</tr>
<tr>
<td>PANSS General</td>
<td>26.65</td>
<td>8.16</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:** PANSS; Positive and Negative Syndrome Scale

#### 4.1.2. Procedures

**4.1.2.1. Symptomatology**

Symptom severity was measured with the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). The PANSS is a 30-item semi-structured interview designed to assess five symptom categories associated with schizophrenia: positive symptoms (i.e., hallucinations and delusions), negative symptoms (i.e., avolition and anhedonia), cognitive symptoms (i.e., thought disorder), hostility, and depression. One trained and calibrated rater assigned a score from 1 to 7 for each item, with higher scores indicating more severe psychopathology.

**4.1.2.2. Social functioning assessment**

The Social Functioning Scale (SFS; Birchwood et al., 1990) measures social engagement/withdrawal (e.g., how often will you start a conversation at home?); interpersonal communication (e.g., how easy or difficult do you find talking to people at present?); independence/performance (e.g., how often do you prepare and cook a meal?); recreation (e.g., how often do you play a sport?); prosocial activities (e.g., how often do you visit friends?); independence/competence (e.g., how able are you to budget?); and employment/occupation (e.g., when were you last employed?). This 79-item questionnaire was completed by a trained interviewer. Items are rated on a 4-point scale of frequency or ability, with higher scores indicating greater competency.
4.1.2.3 Social isolation assessment

Social isolation was measured using the Medical Outcomes Study Social Support Survey (MOS-SSS), developed by (Sherbourne and Stewart, 1991). The MOS-SSS follows the logic of functional support, which divides support into four categories: (a) tangible support, (b) affectionate support, (c) positive social interaction support, and (d) emotional or informational support. The questionnaire consists of 15 items plus one question; the patient was first asked to write the names of a number of close friends and close relatives. The patients were asked to rate the perceived availability of support using a 5-point Likert-type scale rated from 1 (none of the time) to 5 (all of the time). Scores were obtained by summing responses, with a range of possible scores from 15 to 75. Higher scores represent better social support.

4.1.2.4. Perceived stress evaluation

The State–Trait Anxiety Inventory (STAI; Spielberger, 1989) was utilized as the measure of anxiety. For the 20 State items, the patients were asked to respond the number that best describes “how they feel now” with the following 4-point intensity scale: 1 (not at all), 2 (somewhat), 3 (moderately so), and 4 (very much so). For the 20 Trait items, the patients were asked to respond with the number that best describes, “how they generally feel” with the following 4-point frequency scale: 1 (almost never), 2 (sometimes), 3 (often), and 4 (almost always). Accordingly, the mean trait anxiety score of the sample was 49.03±6.41.

4.1.2.5. Psychosocial stress test

A modified version of TSST was conducted to evaluate the stress response of the patients under a condition, which is close to real-life. The TSST procedure has been described in detail elsewhere (Kirschbaum et al., 1993). In the general procedure, the psychosocial stressor consisted of giving an unstructured public talk in front of evaluators who are neutral in expression, while also being recorded on video. Although in our experiment, instead of a public talk, we preferred to use a structured mock job interview. Participants were asked to select one of 6 jobs for which they would be applying for in the interview. Following that, we presented the participants with 5 questions and they were instructed that they will be expected to answer these questions in the interview. They had 10
minutes to prepare their answers (Preparation-Anticipation part lasted 10 minutes). The questions consisted of (1) “Tell us about yourself?” (2) “Why do you think this job is suitable for you?” (3) “What kind of difficulties you may experience in this job?” (4) “Describe a narrative in your life in which you coped with successfully?” (5) “Do you have any questions regarding your application?” In the performance part (lasting 10 minutes), a neutral interviewer asked these questions while another interviewer was sitting next to him and taking notes. Following each question and answer, and after waiting for a fixed amount of time, participants were further informed that they still had time to answer. Time blocks and procedures of the original TSST were strictly followed for the rest of the test. Two calibrated interviewers who were blind to the patient’s job selection evaluated all tests. The experiment finished with a debriefing session (lasting 10 minutes). The reasons for using a structured mock job interview was considering the cognitive impairment and core symptoms in schizophrenia, we believed that expecting free speech from psychotic patients, as used in the original TSST, would be too demanding. Finally, in the original TSST the behavior of participants was videotaped, whereas we used audio recording, based on considerations that video-recording might have had a detrimental effect in paranoid patients.

4.1.3. Experimental procedure

All patients were invited to the clinic 60 minutes before the experiment to complete the self-report measurements. The psychosocial stress tests were performed between 11:00 a.m. and 3:00 p.m., because of the slow descent in cortisol levels at this time of day and peak pulsatile release of oxytocin (Amico et al., 1983; Smyth et al., 1997). Patients were asked to refrain from eating or doing physical exercise 60 minutes before the beginning of the protocol and during the experiment. Before the preparation part (0 min), and right after performance part (20 min), the STAI was filled out to determine fear and anxiety before and after the performance part. The whole testing session took approximately 2 hours. Additionally, heart rate change of the participants was measured by a pulse oxymeter before the preparation part and immediately after the performance part.

4.1.4. Blood sample collection and assessment

Blood samples were collected through a peripheral venous catheter which was inserted in the forearm 60 minutes before the first blood sample was taken to prevent potential stress induction caused by catheterization.
4.1.4.1 Plasma cortisol assessment

Five cubic centimeters of blood were drawn from the catheter into the EDTA tubes once before the preparation (0 min) and once after the performance part (20 min) of the stress test. These time points were selected based on the peak cortisol increase after TSST, relative to baseline, found in previous studies using repeated measures of salivary and plasma cortisol levels (e.g., Kirschbaum et al., 1999). Samples were centrifuged at 4°C at 4000 g for 20 min to separate plasma. Serum cortisol levels were measured by a chemiluminescent immunoassay method, (UniCel DXI 800 Immunoassay System, Beckman Coulter) using Access Cortisol reagent (Beckman Coulter, Inc., Brea, CA) with the minimal detection limit of 0.4 μg/dL (11 nmol/L). Intra-assay and interassay coefficients of variation were respectively 4.4% and 6%.

4.1.4.2 Plasma oxytocin assessment

To measure basal oxytocin levels, another five cubic centimeters of blood were collected before the beginning of the experiment to EDTA tubes containing the polypeptide aprotinin (EDTA-Aprotinin Tubes, Greiner Bio-One GmbH, Germany) and centrifuged at 4°C at 4000 g for 20 min after which plasma was separated into two tubes. Plasma was stored in a freezer at -80°C until the assessment day and assayed as duplicate. For the analyses, considering the debate on the plasma extraction procedure (Szeto et al., 2011), we preferred to use a novel commercially available extraction-free Elisa kit (Bachem S-1355 Oxytocin - EIA Kit, Extraction-free CE-marked). For human serum or plasma samples, typical sensitivity (Av. IC50) was 0.15 ng/ml with a range of 0-10 ng/ml.

4.1.5 Data Analyses

Distributions of all variables were examined to check for the assumptions of parametric statistics in the preliminary step. Oxytocin, cortisol levels and cortisol reactivity to stress index (percentage of cortisol change relative to the baseline) were checked for outliers, defined as 2.5 SD above or below the mean for each assessment. Thus, we found 2 subjects with extreme cortisol reactivity index and replaced their values with the upper limit of the population range to ensure the normal distribution. The validation of the modified TSST was tested by paired t-tests using pre and post stress levels of plasma cortisol, heart rate and state anxiety scores. Similar to previous studies using the TSST (e.g. Roelofs et al., 2005),
individual differences in outcome variables were first statistically evaluated with a categorical approach by a median split procedure of the cortisol reactivity to stress indexes. A binary logistic regression was performed to test the relationship between oxytocin and stress induced cortisol response groups. Differences in the demographic, clinical, hormonal, and behavioral outcome variables between cortisol response groups (i.e. a group with cortisol responses below the median, and a group with cortisol responses higher than the median) were tested with separate ANOVAs. In the second step, we further explored the associations among the study outcome parameters by using pearson correlation analyses followed by a multiple hierarchical regression for identifying the predictors of social functioning. P-values less than .05 were considered significant.

4.2. Results

4.2.1. Baseline gender effect

No significant differences were found for the gender and basal oxytocin (F(1,31)=1.71, p=.20), basal cortisol (F(1,31)=1.98, p=.17) and post-stress levels of cortisol (F(1,31)=.95, p=.34).

4.2.2 Validation of modified TSST as stressful

Relative to the baseline, separate paired t-tests showed significant differences for plasma cortisol levels (t(1,31)=2.33, p=.02) and heart rate (t(1,31)= 2.86, p=.008) following the stress induction though this was not the case for behavioral measures of state anxiety (t(1,31)= 0.05, p=.96). The mean baseline and stress related cortisol responses were 127.67±49.84 and 139.28 ±51.08 (nmol/L) respectively.

4.2.3. Cortisol response groups to stress

Patients below the median cortisol response showed a 4.74 (SE: 1.67) percentage decrease after stress relative to baseline (i.e. cortisol non-responders), whereas patients above the median showed 34.11 (SE: 11.17) percentage increase (i.e. cortisol non-responders group). A repeated measures ANOVA including the gender and the groups as fixed factors and cortisol levels as repeated continuous variables showed a significant 2-way interaction effect between responder groups and raw cortisol levels before and after stress (F(1,31)= 22.12, p<0.001). Notably, there were no effects of gender between groups (F(1,31)= 0.02,
Post hoc t-tests revealed a significant difference ($t= 4.43, p=.001$) relative to the baseline only for the cortisol responder group but not the non-responders. Although there appears to be a difference on basal cortisol levels between groups, this was not reaching significance (See Figure 4.1; $t= 1.56, p=.12$). The raw plasma cortisol changes between groups are illustrated in figure 4.1.

**Figure 4.1:** Means (and standard errors) illustrating the change of cortisol levels after the social stress induction, with a group split of cortisol responders and non-responders.

![Graph showing cortisol levels](image)

**Notes:** Pre; Before the preparation part 0 min, Post: After the performance part, 20 min. Error bars were created based on one standard error.

### 4.2.4. Relationship between oxytocin and cortisol

There was a significant difference on baseline oxytocin levels ($F(1,31)= 3.96, p=.052$) between groups, with the cortisol non-responders group having lower baseline oxytocin levels ($202.88\pm 79.56$ pg/ml) when compared to cortisol responders ($292.50\pm 161.42$ pg/ml). Oxytocin levels for subjects in each group are plotted in figure 4.2. Following the linear correlations, curvilinear regression between oxytocin and cortisol reactivity to stress revealed a better model fit with quadratic function ($F(2,29)= 1.525, p=.23$), instead of a linear function.
(F(2,29)=.025, p=.87; see table 4.2 and Figure 4.3). The linear correlations between oxytocin and cortisol reactivity was not significant (r=.03; p=.87). To further explore the relationship, a binary logistic regression model for predicting cortisol responder groups by oxytocin showed significant model reliability (Wald $\chi^2(1)= 4.01$, p=.04) and classified 59.4% of the cases. We found that the independent role of plasma oxytocin levels in the model was approaching significance (p=0.06) with an odds ratio of 1.006. Plasma oxytocin levels were better in classifying the blunted cortisol response group (68%) when compared to the increased cortisol response group (50%).

**Figure 4.2:** Box plot of oxytocin levels for each subject within cortisol responder and non-responder groups to psychosocial stress.
Figure 4.3: Scatter plot between the oxytocin levels and the cortisol reactivity index

Table 4.2: Curvilinear regression results between oxytocin and cortisol reactivity

<table>
<thead>
<tr>
<th>Equation</th>
<th>Model Summary</th>
<th>Parameter Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R²</td>
<td>F</td>
</tr>
<tr>
<td>Linear</td>
<td>.001</td>
<td>.025</td>
</tr>
<tr>
<td>Quadratic</td>
<td>.095</td>
<td>1.525</td>
</tr>
</tbody>
</table>

4.2.5. Group differences between behavioral measures of social support and social functioning.

The between group differences and the p values on measures of social support and social functioning are summarized in table 4.3. Accordingly, significantly higher social functioning scores were observed for the cortisol responder group on the interpersonal communication, prosocial activities, recreation activities, and independence/performance subscales. Interestingly, non-cortisol responders exhibited a lower number of close
relationships as compared to responders, which appears to be approaching statistical significance. With regard to medication, symptomatology and anxiety there were no differences between the groups in terms of mean trait anxiety score (F(1,31)= 1.47, p=.23), mean chlorpromazine equivalents (F(1,31)= 2.61, p=.12), negative (F(1,31)= 1.14, p=.29), positive (F(1,31)= 0.13, p=.73) and general symptoms (F(1,31)= 0.04, p=.83) according to PANSS scores.

Table 4.3: Group difference on measures of trait anxiety, social support, and social functioning

<table>
<thead>
<tr>
<th>Cortisol response groups</th>
<th>Non-responders</th>
<th>Responders</th>
<th>F Value (df)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFS- social engagement/withdrawal</td>
<td>10.88</td>
<td>10.34</td>
<td>.398(1,31)</td>
<td>.533</td>
</tr>
<tr>
<td>SFS- interpersonal communication</td>
<td>5.38</td>
<td>7.19</td>
<td>5.181(1,31)</td>
<td>.030</td>
</tr>
<tr>
<td>SFS- prosocial activities</td>
<td>13.50</td>
<td>19.44</td>
<td>4.269(1,31)</td>
<td>.048</td>
</tr>
<tr>
<td>SFS- recreation</td>
<td>14.38</td>
<td>19.06</td>
<td>4.862(1,31)</td>
<td>.035</td>
</tr>
<tr>
<td>SFS- independence/competence</td>
<td>31.38</td>
<td>34.44</td>
<td>1.557(1,31)</td>
<td>.222</td>
</tr>
<tr>
<td>SFS- independence/performance</td>
<td>23.06</td>
<td>28.94</td>
<td>4.301(1,31)</td>
<td>.047</td>
</tr>
<tr>
<td>SFS- employment/occupation</td>
<td>6.88</td>
<td>7.69</td>
<td>.548(1,31)</td>
<td>.465</td>
</tr>
<tr>
<td>MOC number of close relationships</td>
<td>3.38</td>
<td>5.94</td>
<td>3.334(1,31)</td>
<td>.078</td>
</tr>
<tr>
<td>MOC Tangible Support</td>
<td>13.81</td>
<td>14.38</td>
<td>.152(1,31)</td>
<td>.699</td>
</tr>
<tr>
<td>MOC emotional or informational support.</td>
<td>26.44</td>
<td>29.13</td>
<td>1.48(1,31)</td>
<td>.232</td>
</tr>
<tr>
<td>MOC affectionate support</td>
<td>10.88</td>
<td>11.69</td>
<td>.59(1,31)</td>
<td>.446</td>
</tr>
<tr>
<td>MOC positive social interaction support.</td>
<td>14.69</td>
<td>14.19</td>
<td>.181(1,31)</td>
<td>.674</td>
</tr>
</tbody>
</table>
4.2.6. Correlations

The correlation coefficients between the behavioral measures derived from the social functioning, social support, and the STAI scales and the hormones were summarized in Table 4.4. Accordingly, basal cortisol levels showed inverse significant correlations with the positive social interaction subscale of social support survey (p=0.057) and the occupational functioning subscale of social functioning scale (p=0.051). Cortisol reactivity to social stress was positively correlated with interpersonal relationship, recreation activities and independence-performance subscales of social functioning. Unexpectedly, oxytocin levels were in negative association with social functioning subscales, although this was only significant for social withdrawal subscale (p=.015). Equally interesting, plasma oxytocin levels were also in negative relationship with the general symptoms on the PANSS scale (p=.051). Regarding the social support, the number of close friends and relations had significant positive correlations with interpersonal relationships and prosocial activities of social functioning scale. In addition, informational or emotional support was in positive association with interpersonal relationships subscale of social functioning. As expected, negative correlations were noted between the social functioning subscales and symptom severity. Lastly, among the perceived stress assessments, only post TSST state anxiety was positively correlated with the cortisol reactivity to stress (r=.35; p=.052).
### Table 4.4: Inter-correlations among the behavioral measures derived from the different scales and the endocrine measures.

|          | 1   | 2   | 3   | 4   | 5   | 6   | 7   | 8   | 9   | 10  | 11  | 12  | 13  | 14  | 15  | 16  | 17  | 18  | 19  |
|----------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 1. Basal |     | 1   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Cortisol |    -.20 | 1  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 2. Cortisol reactivity (%) | .03 | .03 | 1   |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| Oxytocin |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 4. SFS-SWI | -.09 | .07 | -.43 | .1  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 5. SFS-IPL | -.32 | .40 | -.09 | .37 | .1  |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 6. SFS-PSA | -.10 | .31 | .09 | .29 | .66 | .1  |     |     |     |     |     |     |     |     |     |     |     |     |     |
| 7. SFS-RC | -.10 | .45 | -.09 | .08 | .39 | .49 | .1  |     |     |     |     |     |     |     |     |     |     |     |
| 8. SFS-INP/COMP | -.24 | .27 | -.11 | .36 | .46 | .43 | .38 | .1  |     |     |     |     |     |     |     |     |     |     |
| 9. SFS-IND/PER | -.22 | .46 | -.22 | .35 | .69 | .61 | .47 | .67 | .1  |     |     |     |     |     |     |     |     |     |
| 10. SFS-OCC | -.35 | .22 | -.25 | .42 | .67 | .47 | .20 | .54 | .61 | .1  |     |     |     |     |     |     |     |     |
| 11. MOC-CR | -.26 | .15 | -.23 | .34 | .56 | .55 | .12 | .20 | .39 | .50 | .1  |     |     |     |     |     |     |
| 12. MOC-TS | -.23 | -.18 | -.09 | -.05 | .01 | .03 | .02 | .19 | .07 | .07 | .06 | .1  |     |     |     |     |     |
| 13. MOC-EIS | -.29 | .14 | .03 | .11 | .40 | .17 | .20 | .28 | .36 | .28 | .16 | .44 | .1  |     |     |     |     |
| 14. MOC-AS | -.18 | .02 | .10 | -.11 | .07 | .04 | -.14 | .03 | -.02 | -.18 | .20 | .39 | .56 | .1  |     |     |
| 15. MOC-PSI | -.34 | -.16 | -.08 | .27 | .30 | .12 | -.27 | .14 | .18 | .27 | .35 | .55 | .67 | .67 | .1  |
| 16. PANSS | .03 | -.20 | .03 | -.39 | -.36 | -.12 | -.03 | -.17 | -.20 | -.39 | -.05 | .05 | -.10 | -.05 | -.17 | .1  |
| Positive | 17. PANSS | .23 | -.26 | .20 | -.45 | -.66 | -.36 | -.43 | -.41 | -.62 | -.62 | -.32 | -.02 | -.25 | .14 | -.11 | .52 | .1  |
| Negative | 18. PANSS | .22 | -.17 | .35 | -.39 | -.59 | -.22 | -.19 | -.18 | -.41 | -.45 | -.25 | .09 | -.34 | -.14 | -.27 | .74 | .68 | .1  |
| General | 19. CPZ | .02 | -.28 | .04 | -.15 | -.13 | -.14 | .00 | -.22 | -.13 | -.21 | .01 | -.07 | -.30 | -.08 | -.11 | .31 | .33 | .22 | .1  |

**Notes:** SFS; Social functioning scale. MOC; Medical Outcomes Study Social Support Survey. SWI; withdrawal. IPL; Interpersonal relationship. PSA; Prosocial activities. RC;
Recreation activities. INP/COMP; Independence competence. OCC; Occupation and employment. CR: Number of close relationship TS; tangible support. EIS; emotional or informational support. AS; affectionate support. PSI; positive social interaction support. PANSS; positive and negative symptom scale in schizophrenia. CPZ equivalent; chlorpromazine equivalent.

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

### 4.2.7. Predictors of social functioning

Several hierarchical regression analyses for each subscale of social functioning were conducted in this step. Independent variables were selected according to the Pearson correlation analyses. Correlations with a smaller p value from .1 were selected as potential predictors and thus included to the regression analyses. The models with the highest R values were considered as the best models and presented below. Accordingly, we found that social withdrawal was significantly predicted by plasma oxytocin levels, although oxytocin levels did not predict the rest of the social functioning subscales. Cortisol reactivity to social stress significantly predicted interpersonal relationships, recreation activities and independence/performance subscales of social functioning. Although not independently, basal cortisol levels were successful in explaining the independence/competence and occupation/employment subscales. Equally interesting, perceived change in the anxiety to the TSST has contributed in explaining recreation activities and occupational functioning. Lastly, significant independent contributions came from the number of close relationships and emotional/informational support subscales of social support to explain interpersonal relationships, prosocial activities and independence/performance and occupational social functioning in our sample. The results of the regression analyses were summarized in table 4.5.

Lastly, as a note of caution, a summary of the main findings of this study was presented in Chapter 5.
Table 4.5: Predictors of social functioning

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Variance</th>
<th>Analysis</th>
<th>Coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2$</td>
<td>$R^2_{corr}$</td>
<td>F</td>
</tr>
<tr>
<td><strong>1. Withdrawal</strong></td>
<td>.170</td>
<td>.139</td>
<td>5.11</td>
</tr>
<tr>
<td><em>Plasma Oxytocin</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2. Interpersonal Relationship</strong></td>
<td>.393</td>
<td>.346</td>
<td>8.41</td>
</tr>
<tr>
<td><em>Cortisol reactivity</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>MOS-Close relationships</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>3. Prosocial activities</strong></td>
<td>.238</td>
<td>.210</td>
<td>8.46</td>
</tr>
<tr>
<td><em>MOS-Close relationships</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>4. Recreation activities</strong></td>
<td>.27</td>
<td>.223</td>
<td>4.98</td>
</tr>
<tr>
<td><em>Cortisol reactivity</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>STAI difference</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>5. Independence/Competence</strong></td>
<td>.260</td>
<td>.171</td>
<td>3.41</td>
</tr>
<tr>
<td><em>Basal Cortisol</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>STAI difference</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>STAI Trait</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>6. Independence/ Performance</strong></td>
<td>.390</td>
<td>.343</td>
<td>8.31</td>
</tr>
<tr>
<td><em>Cortisol reactivity</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>MOS-EIS</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>7. Occupation/Employment</strong></td>
<td>.326</td>
<td>.254</td>
<td>4.51</td>
</tr>
<tr>
<td><em>MOC-Close relationships</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>MOC-EIS</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Basal Cortisol</em></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: SFS; Social functioning scale. MOC; Medical Outcomes Study Social Support Survey. EIS; emotional or informational support.

4.3. Interim Discussion

A group of individuals that are particularly vulnerable to stress are those diagnosed with schizophrenia (Demjaha et al., 2012). In fact, a substantial body of research has demonstrated altered HPA axis in schizophrenia, which has also been suggested to be one
potential contributor for the development of the illness (reviewed in Bradley and Dinan, 2010). A large body of research has investigated individual differences in stress-coping mechanisms at the neurophysiological and neurochemical levels in schizophrenia. It is now generally accepted that it is not only the basal levels of cortisol that is involved in the adaption to stress, but also its reactivity to stress which together with the neuropeptide oxytocin, plays a crucial role in maintaining the homeostasis of behavioral, cognitive and neuroendocrine functions (Meyer-Lindenberg et al., 2011). Considering the lack of social support and impairments in social functioning that patients with schizophrenia often experience, this syndrome provides a relevant model to explore the relationship between cortisol and oxytocin in response to stress.

The implications of basal cortisol levels have been extensively studied in various psychiatric and somatic disorders as well as patients with schizophrenia. A substantial number of studies have designated the higher basal cortisol activity as an indicator of chronic stress, social isolation and severity of illness in schizophrenia. Basal HPA hyperactivity is a well-replicated finding in patients with schizophrenia (Mittal et al., 2007; Walder et al., 2000; Walker et al., 2002; Walker et al., 2001). For instance, Walder and his colleagues (2000) found that basal cortisol levels of schizophrenia patients were inversely correlated with neurocognition and symptom severity. Ritsner et al. (2007a) followed similar lines and evaluated the early morning plasma concentrations of cortisol, dehydroepiandrosterone and its sulfate derivate in schizophrenia. The patient group exhibited significantly higher state and trait anxiety, anger expression index, and emotional and somatic self-reported distress scores in this study. Regarding the plasma concentrations, the patient group displayed: first, higher biological stress markers; and second, these markers correlated with duration of illness, state and trait anxiety, trait anger and hostility (Ritsner et al., 2007a; Ritsner et al., 2007b). Notably, antipsychotic treatment dosage and symptom severity were not associated with any of the plasma markers in the Ritsner et al. study (2007a). The results of Study 3 are in line with previous findings in regards to the basal cortisol activity, because it demonstrated that occupational functioning in schizophrenia is inversely correlated with basal cortisol levels. Furthermore, the categorical approach in Study 3 revealed that patients below the median levels of cortisol reactivity had higher basal cortisol levels, yet with higher social isolation and poorer social functioning. Although the correlations between the basal cortisol levels and other social functioning and social support domains were mostly not statistically significant,
they showed a trend in the negative direction, which further suggests a worsening of functionality linked with higher basal cortisol activity.

In regards to the cortisol reactivity to stress, both physiological and psychosocial stimulations have been utilized in schizophrenia. For instance, Albus et al. (1982) conducted a cold pressor test (immersion of a limb in iced water) to a group of schizophrenia patients and healthy controls. They found that although throughout the experiment schizophrenia patients exerted higher levels of physiological and biological stress as measured by plasma cortisol and epinephrine levels, their situational response to stress was significantly lower than that of healthy controls. In addition, Goldmann et al. (2007) utilized the same test and replicated the findings of Albus et al. In addition, they also measured the ACTH levels of the participants before and after the stress, which they found to have a lower reactivity in the patient group as compared to the healthy controls. Interestingly, Brier et al. conducted another study in 1988 in which they measured the cortisol and ACTH levels of schizophrenia patients and healthy controls during a lumbar puncture (a stressful method for collecting CSF samples from intervertebral space). They found that control subjects but not schizophrenics had a significant increase in the ACTH and cortisol levels. Equally interesting, higher ACTH and cortisol levels related to stress were associated with lower levels of symptom severity in the schizophrenia group. In fact, the Brier et al study underlined the heterogenic nature of schizophrenia patients and the in-group differences in regards to cortisol reactivity to stress. Meltzer et al., (2001) conducted another study in which cortisol and ACTH response to intravenous administration of a dopaminergic agonist (apomorphine) was evaluated. The authors demonstrated that schizophrenia patients in general had lower cortisol responses as compared to healthy participants. However, higher cortisol responders in the schizophrenia group presented successful treatment outcome following antipsychotic treatment. Taken together these studies clearly suggest within group differences in the biological response to stress, which has potential to explain functioning in schizophrenia.

Furthermore, as mentioned in the introduction, a few studies have evaluated the cortisol reactivity to stress response of schizophrenia patients by utilizing the TSST (Brenner et al., 2009; Jansen et al., 1998; Pruessner et al., 2013). Notably, none of these studies evaluated the ingroup differences and their implications on functioning in schizophrenia. Nevertheless, all of these studies found a non-significant increase of cortisol levels following the TSST. However, they also clearly mention that they were not able to conclude a blunted cortisol response in schizophrenia as a distinctive finding because of the observed ingroup
differences in the schizophrenia group (see Brenner et al., 2009). Thus, one of the main purposes of this study was to enlighten the functional effects of varying cortisol reactivity to stress in schizophrenia.

Most interestingly, the results of study 3 demonstrated an in-group difference in social functioning such that higher cortisol reactivity was related with better social functioning, which is also supported by multivariate statistics. Studies on depressed or socially anxious individuals without psychosis have demonstrated a supranormal cortisol response, which has a negative influence on general social functioning, in comparison to healthy controls (Elzinga et al., 2010; Hoge et al., 2013; Tyrka et al., 2007). Therefore, it seems to be the case that those detrimental effects of abnormal cortisol levels on social functioning may not only be related to excessive cortisol response, but also to the blunted cortisol response to stress. Taken together, both supranormal and blunted cortisol responses to social stress may cause a neurobiological dysregulation (de-synchronization), whereas a moderately increased cortisol response may correspond to a more functionally beneficial response to stress (Joels et al., 2006).

A recent animal study revisited the inverse “U” shaped relationship between learning and the biological stress response in rats (Salehi et al., 2010). Accordingly, they demonstrated that both low and extremely high levels of stress negatively influence learning and memory. Accumulating evidence from neuroimaging studies suggests that stress alters the activation of a neural network including the amygdala, hippocampus, and prefrontal cortex (Joels et al., 2006). Interestingly, these areas are also activated during the processing of information associated with a stressful event (Van Stegeren et al., 2010). Taken together, these studies suggest that stress-induced release of corticosteroid hormones is necessary to synchronize (normalize) the activity of the above-mentioned circuits involved in the processing of information linked to the event (Joels et al., 2006). It seems to be that both the initial stress and the induced activation of this network are required for learning and performing under stress. Therefore, a moderate cortisol response to stress may be critical to help the organism maintain homeostasis and improve social functioning (Allman, 1999)

In the literature, several studies on cortisol reactivity to stress in schizophrenia have compared their findings with healthy populations and have concluded the presence of a blunted cortisol reactivity to stress in schizophrenia as a general finding (Brenner et al., 2009; Jansen et al., 1998; Meltzer et al., 2001; Pruessner et al., 2013). In terms of causal effects of cortisol response to stress, only one study demonstrated negative consequences of cortisol
reactivity to stress in the individuals’ satisfaction with their life (as a measure of quality of life; QoL) in schizophrenia (Brenner et al., 2011). Interestingly, they found that patients who present a lower cortisol reactivity to the TSST reported higher QoL. Accordingly, the authors concluded that a blunted stress response might be a precondition under which certain types of coping strategies might be associated with a greater sense of well-being in schizophrenia. In contrast, the results of the present study (Study 3) suggest that higher cortisol reactivity enhances successful social functioning in schizophrenia. In fact, the Brenner et al. (2011) evaluated coping strategies of the patients by asking them about their potential behavioral response to an event in which they win the lottery with a friend and their friend escapes afterwards. The patients who preferred to do nothing presented also better perceived life satisfaction, whereas patients who used active strategies to cope with the situation, such as calling the police, presented low life satisfaction. Looking from another perspective, passive coping strategies were related to blunted cortisol response whereas active coping strategies were related to a moderate increase on the cortisol levels after the psychosocial stress induction. Taken as a whole, it is plausible to argue that active coping strategies in the presence of high cortisol reactivity may have enhanced social functioning in Study 3.

According to the social buffering hypothesis, oxytocin inhibits the HPA response, which is referred to as the buffering effects of oxytocin on stress. Conversely, the results of Study 3 support the fine-tuning effects of oxytocin on social stress, because higher basal oxytocin levels were related to significant cortisol reactivity to stress in this study. Oxytocin is secreted from the hypothalamus and shares similar neurophysiological pathways with the areas responsible for the regulation of the HPA axis (reviewed in Herman et al., 2002). Goldman et al. (2008) reported that the activity of the central negative HPA feedback mechanism was positively correlated with plasma oxytocin levels in schizophrenia. In other words, with a cold suppressor test, the ACTH levels following the cortisol peak were positively associated with oxytocin levels. It is possible that a lack of a normalizing (synchronization) effect of oxytocin, particularly in those schizophrenia patients with lower basal oxytocin levels, consequently results in an inadequate cortisol response to stress, and this would have had a negative influence on social functioning. Alternatively, an attenuated cortisol response to stress associated with lower plasma oxytocin levels may have limited the activation of cognitive faculties under stress (Cornelisse et al., 2011), consequently leading to poorer social functioning.
As also mentioned in the introduction, several studies evaluating the role of oxytocin on cortisol reactivity found stress-reducing effects of oxytocin. However, neuroendocrine interactions usually do not show a linear relationship (Fink, 2007). In general, a negative and a positive feedback valve mechanism play a crucial role in designating a delicate balance between neuroendocrine hormones (Fink, 2007). This may explain why we could not find linear correlations between cortisol reactivity to stress and oxytocin levels in schizophrenia, though such correlation was present in non-psychiatric populations as mentioned in the introduction (see Pierrehumbert et al., 2012). Nevertheless, although not significant, we demonstrated that the endocrine interaction between oxytocin and cortisol fits better to a quadratic equation instead of a linear one, which means both extreme poles in the cortisol reactivity scores were related with lower oxytocin levels. The U-shaped effect of oxytocin has been shown in a study where trust behavior was assessed in healthy participants. Zhong et al., (2012) found that moderate levels of oxytocin were related with appropriate trust behavior, whereas both low and extreme trust behavior (dysfunctional) was related to extreme low and high oxytocin levels. In addition, the non-linear effect of oxytocin on cortisol response was demonstrated also by administration of oxytocin in a recent study (Cardoso et al., 2013). It is clear that these explanations are partially speculative. Hence, the findings of Study 3 on oxytocin and cortisol interactions must be replicated and more information should be gathered on the physiologic regulation of stress in schizophrenia. For example, studies evaluating neuropeptides in schizophrenia have typically found differences in vasopressin and oxytocin interactions (Linkowski et al., 1984; Teltsh et al., 2013). Considering that also vasopressin has a significant impact on stress regulation (Neumann et al., 2008), studying this interaction in schizophrenia may support the findings of Study 3.

Social support has been found to be an important predictor of psychosocial stress and oxytocin levels in previous studies (Heinrichs et al., 2003). Ditzen et al. (2007) found that active social support by physical contact or face-to-face interaction reduced the stress-induced cortisol response as well as behavioral measures of stress. However, we did not find any significant effects of social support on cortisol reactivity and oxytocin levels in our population. One explanation could be that the social support received by a group of patients with schizophrenia may not be fulfilling social needs and perceived value (Milne, 1999). This is particularly relevant in chronic clinical populations that are usually actively supported by healthcare professionals and families, but may not be benefitting from the social interaction due to the lack of intimacy as a result of the nature of the social relationships (Slevin et al.,
2003). In fact, the negative correlation between positive social interaction and basal cortisol levels, which approached significance, may support this speculation. Alternatively, previous experiences that have had a substantial negative impact on the development of social support, such as childhood trauma, had a more predominant influence when compared to the actual status of social support. The previously described detrimental effect of chronic trauma on oxytocin (Heim et al., 2009; Pierrehumbert et al., 2010), and cortisol levels (Flory et al., 2009) may support this explanation. These neurobiological interactions may also help to explain the low levels of social functioning seen in patients with schizophrenia who have had a history of trauma (Lysaker et al., 2001).

Notably, an unexpected inverse correlation between oxytocin and social withdrawal was demonstrated in the present study (Study 3). In addition, patients with higher oxytocin levels showed less general symptoms and this reduced symptom severity was associated with less social withdrawal in our sample. Social withdrawal in this study was measured with a social functioning scale in which higher social withdrawal was indicated as lower scores (Birchwood, 1991). To measure social withdrawal, participants were asked to respond to several likert scaled items, which generally question the degree of loneliness of the participant and his or her active or passive strategies to avoid social interactions. According to a recent study, social withdrawal in schizophrenia is not merely a product of psychotic symptoms, and may have come from similar roots as the non-schizophrenic individuals (Velthorst et al., 2012). In healthy populations, social withdrawal may indicate a coping mechanism that protects the self from environmental threats. For instance, Seiffge-Krenke et al. (2008) found that high perceived stress is associated with withdrawal symptoms in young people independent from the nature of the social situation. A group of individuals who actively avoid social interactions is patients with social anxiety disorder (SAD). A thought provoking study found higher levels of plasma oxytocin to be associated with higher social anxiety in patients with SAD (Hoge et al., 2008). The researchers explained this unexpected finding by reasoning that this was due to a compensatory increase of oxytocin levels under social interaction, because in their study plasma levels of oxytocin were collected just before the completion of self-report questionnaires and hence a social interaction with the interviewer had already started. Therefore, the high oxytocin levels in a subgroup of SAD patients may have occurred as a buffering effect in order to avoid an increase the stress levels and thus facilitate social interaction, although it is plausible that this buffering may fail in this subgroup. A similar explanation may also apply to the negative correlations between
oxytocin, social withdrawal and symptom severity in Study 3. Accordingly, the patients who were enrolled in Study 3 were aware that they would be participating in an experiment when they first arrived to the clinic. Therefore, the group of patients who had less general symptoms yet high social withdrawal and avoidance may have had higher oxytocin levels before the experiment took place as a biological coping strategy. The rest of the social functioning domains were not significantly correlated with oxytocin. Thus, this unexpected finding may not be attributed to the psychometric properties of SFS. Despite all, this explanation needs confirmation in a study where plasma oxytocin levels of schizophrenia and SAD patients are compared. Otherwise, this interesting finding in Study 3 is not sufficient to draw firm conclusions.

Lastly, the hierarchical regression analyses that explored predictors of social functioning in schizophrenia highlighted the number of close relations, emotional support, perceived stress, basal cortisol levels, and cortisol reactivity to stress as the prominent predictors of social functioning subdomains. To the best of our knowledge, Study 3 is the first study evaluating the effects of biological and social predictors on social functioning. The regression analyses supported our previous explanations about the causal role of biological stress regulation and social support. As expected, basal cortisol levels predicted the outcome in the negative direction whereas cortisol reactivity did in the positive direction.

In line with our findings, it is clear that an attenuated or absent cortisol response to stress cannot be generalized to the whole schizophrenia population, as has been previously reported. It appears that there is a subgroup of patients with an intact neuroendocrinological foundation to social stress. The use of oxytocin as adjuvant therapy may therefore be beneficial for some patients with schizophrenia by improving strategies to cope with social stress through neuroendocrine stress regulation. However, this may be dependent on the level of cortisol response to stress in the individual, whereby oxytocin administration may only be effective in improving social functioning in patients who exhibit a sufficient cortisol response to stress profile. Furthermore, cortisol reactivity to stress had significant potential to explain social impairments in schizophrenia in Study 3. Although there are no similar studies in schizophrenia populations, one study found basal cortisol levels to be predictor of poor informational processing in schizophrenia (Halari et al., 2004). Taken as a whole, the results of study 3 provide evidence that the interplay between the cortisol response to stress and oxytocin should be taken into consideration in future studies exploring the potential effects of oxytocin administration on social functioning performance in a schizophrenia population.
Moreover, cortisol reactivity to social stress in schizophrenia may have potential to predict treatment outcome and social performance in schizophrenia. Nevertheless, these preliminary results are sufficiently promising to warrant further testing of biological predictors of stress regulation in schizophrenia.
CHAPTER 5 - GENERAL DISCUSSION

The detailed discussion of the results for each study has been included at the end of each of the last three chapters. Now, there will first be a summary of the main findings followed by a discussion of more general interpretations and implications of these studies.

5.1. Summary of the main findings

5.1.1 Study 1

Study 1 sought to examine the relationship between intrinsic motivation and metacognition, and their impact on learning potential and social functioning in remitted patients with schizophrenia. Here, it has been demonstrated that intrinsic motivation is highly correlated with metacognitive abilities. Specifically, patients who perceived the training as valuable and useful for improving their cognitive skills showed better metacognitive capacity. Interestingly, no correlations between the metacognitive subdomains and the patients’ personal interest and enjoyment from the training were found. Moreover, perceived interest and enjoyment subdomain was in close association with other IMI subdomains such as the perceived usefulness and efforts given to complete the training. As expected, the need for extrinsic motivation was negatively correlated with intrinsic motivation, metacognition, and theory of mind skills. In addition, moderate to low correlation coefficients were observed between ToM and metacognition. Notably, participants who showed more perceived competency presented also higher metacognitive capacity, ToM and intelligence. Lastly, intelligence as measured with MQ only correlated with metacognitive mastery.

When subdividing the schizophrenia sample according to the participants’ learning potential into non-learners, learners and high-achievers, all outcome parameters significantly differed between the high achievers and non-learners. In addition, non-learners showed significantly less intelligence, lesser efforts to complete the training and problems in perceiving the value of the training. In addition to these results, they lacked metacognitive mastery, interpreting other people’s mental states and understanding the influence of external environmental factors on their own social problems. Although high achievers demonstrated superior interest and enjoyment with better metacognitive capacities, these findings were not significant. Lastly, although not significant, learners group presented higher theory of mind skills.
Moreover, learning potential was positively related to metacognition, motivation, and intelligence, but was negatively associated with extrinsic need for motivation. In the last step of the data analyses, the moderators of improvements in WCST performance following specific cognitive remediation training for WCST skills were tested. In the regression model, metacognitive mastery was found to be the best predictor of LP. Although they contribute to the model, both intrinsic motivation and intelligence were not independent predictors of the variance.

Regarding social functioning, occupational functioning was related to the perceived given efforts to complete a training and metacognitive self-reflectivity. ToM skills were related to interpersonal relationships, independence/competence and performance subscales of social functioning, which suggest that better social functioning was engendered by preserved ToM skills. In addition, metacognitive self-reflectivity and decentration predicted the independence and competence subdomain of social functioning in the schizophrenia sample of this thesis.

5.1.2 Study 2

Study 2 sought to explore the effects of oxytocin levels on patients’ potential to benefit from a structured social cognition training. Here, following the training, the patients’ emotion perception, cognitive ToM and externalizing bias improved significantly. Regarding the predictors of outcome, the present study showed that face recognition and discrimination gain scores were related to personalizing and externalizing bias. Although not significant, improvements in face discrimination had positive correlation coefficients with the potential improvements in cognitive ToM skills. Intriguingly, there was an inverse correlation between the patients’ cognitive ToM performance before the training and their gain scores. In other words, patients with lower ToM capacities benefitted more than the patients whose cognitive ToM skills were preserved at baseline.

Regarding the role of oxytocin, there were no correlations between baseline measures and gain scores, except for the face discrimination gain score approaching significance in the positive direction. Nevertheless, the regression analyses showed that higher levels of oxytocin in patients predicted improvements on the emotion perception part of the F-SCIT, and this was particularly observed for the face discrimination test. Accordingly, 32% of the
patients’ face discrimination test-gain scores were explained by plasma oxytocin with non-significant contribution from age and IQ.

5.1.3 Study 3

Study 3 sought to explore the relationship among social isolation, social functioning and basal oxytocin levels between cortisol reactivity to stress in schizophrenia. As expected, the modified version of the TSST appeared to be valid because a significant increase from baseline in heart rate and cortisol levels was observed. Although self-report measures of anxiety did not differ after the TSST in the present study, post-TSST state anxiety positively correlated with cortisol reactivity to stress. As a note, the observed reduction of cortisol levels of the non-responder group following the social stress is a common finding which occurs due to the diurnal fluctuation of plasma cortisol levels (Brenner et al., 2009; Kirschbaum et al., 1993). In line with previous studies in clinically healthy populations, the results of this thesis may also suggest a link between oxytocin levels and the cortisol reactivity to social stress in patients with schizophrenia. Specifically, it has been demonstrated that a group of patients with attenuated cortisol response to social stress had lower basal oxytocin levels. Notably, a curvilinear regression showed a better fit when oxytocin and cortisol reactivity interaction is considered as quadratic instead of a linear equation. Interestingly, patients with relatively higher cortisol reactivity to social stress had higher scores in social functioning, including prosocial activities, interpersonal communication, recreational activities and independent social performance. Unexpectedly, social isolation as measured with a social support survey was not significantly different between groups except on the number of close relationships which approached significance. Equally interesting, basal cortisol levels showed negative correlation coefficients with all social functioning and social support subdomains, although it only reached significance in the case of occupational social functioning. Significantly positive correlation coefficients were noted between the cortisol reactivity to social stress and the interpersonal relationships, the recreation activities and the independent social performance subscales of social functioning. Lastly, oxytocin levels showed significant negative associations with social withdrawal, and general symptoms. The hierarchical regression analyses with the possible predictors of each social functioning subdomain separately revealed that: social withdrawal was significantly predicted by plasma oxytocin levels; interpersonal relations were significantly predicted by cortisol reactivity to stress and the number of close relationships; prosocial activities were significantly predicted by the number of close relationships; recreation activities were significantly predicted by cortisol
reactivity; independence/competence was significantly predicted by trait STAI levels; independence/performance was significantly predicted by emotional or informational support and cortisol reactivity; and lastly, occupational functioning was significantly predicted by the number of close relations. Notably, although not significant, basal cortisol activity and emotional informational support contributed to the model explaining occupational functioning.

5.2. Integrating the results of three studies

The main aim of this thesis was to explore possible pathways that affect social functioning in schizophrenia. Importantly, the findings of this thesis provided preliminary evidence to shed light on the missing parts of social dysfunction puzzle in schizophrenia. It appears to be that although some with small effect, all of the hypotheses were generally confirmed. Specifically, the association between plasma oxytocin levels and cortisol reactivity to stress was not clear enough to permit a firm conclusion to be drawn. Despite the significant group differences, a statistically significant correlation was not present between these variables. As a note of caution, the specific findings of each study were discussed in details during the interim discussions. Hence, the aim of this section is to present hypothetical explanations constructed from the findings of the present thesis and findings of the recent studies. Accordingly, in light of the present findings of this thesis, Rosenfeld model is favored, and an updated model is proposed, which now includes metacognition, motivation, learning and biological response to stress (See figure 5.1).
Notes: EP; emotion perception. Gray arrows indicate previously well-replicated findings and the black arrows indicate main findings of this thesis.

Regarding the specific effects of oxytocin on human social cognition and behavior, considerable efforts seeking the answer in the high-order cortical brain structures have not shown promising result (reviewed in Meyer-Lindenberg, 2011). Concerning the subcortical structures, the amygdala appeared as the most sensitive brain region with its unique features on appraising the emotional valence of sensory information and sending projections to the prefrontal cortex, dopaminergic circuits and the peripheral nervous system to activate a critical brain circuit, which battles against the social barriers of the outer world (Hurlemann et al., 2010). In the past, investigators concluded that the misinterpretation of this sensory input at the amygdala level might alter the high-order ToM and metacognitive bottom up analyses (Corden et al., 2006; Kreifelts et al., 2010; Mier et al., 2010). Therefore, it is plausible to argue that basic-level deficits in emotional processing influenced by oxytocin...
may also contribute to the impaired social behavior observed in schizophrenia such as social withdrawal.

Along similar lines, the Rosenfeld model for schizophrenia (2011) proposed a model in which amygdala plays a central role in response to environmental stimuli. Misinterpretations concerning the salience and intensity of the stimuli lead to an aberrant activation on amygdala, which often signals a stimulus being appraised as threatening. Such threatening stimuli may activate the autonomous nerve system and HPA axis as an initial alarm for setting the adaptation of the organism cognitively and behaviorally. On the other hand, the oxytocinergic system dampens the activations in the amygdala, autonomic nerve system and HPA axis and hence plays a crucial supervisory role on the amygdala and is activated when the stimuli is perceived as prosocial and trustworthy. Rosenfeld et al. further proposed that, activations in the oxytocinergic system act on dopaminergic neurons to assign salience to perceived prosocial stimuli and hence allocate rewarding features to that stimuli. In addition, amygdala and prefrontal cortex interconnections together increase cortical activity, which results with increased visual attention and working memory performance. Such increased activity in amygdala and prefrontal cortex would also trigger theory of mind and social perception related brain areas. Lastly, as a consequence of these sophisticated evaluations originating from amygdala, individuals plan and initiate a behavioral response. However, in schizophrenia, abandoned dopaminergic activity, aberrant reward processing, amygdala dysfunction, and abnormal functional connectivity in the prefrontal cortex decline the assignment of emotional salience and subsequently disenable the healthy activations throughout this cascade. Such declinations would lead to inappropriate or inadequate behavioral response. Taken as a whole, a failure in any part of that system may further give insights to the emotion related symptom clusters in schizophrenia such as social withdrawal, blunted affect, and paranoia. Despite the strengths of Rosenfeld’s integrative model, critical domains that were related to social functioning in schizophrenia such as metacognition, intrinsic motivation, and biological response to stress were somehow neglected. One particular reason for that may be they have proposed a model for explaining behavioral responses, based on misinterpreted emotional salience.

From an evolutionary point of view, adaptation to environmental stimuli is one of the main human characteristics (Allman, 1999). It should however be noted that, the neuronal response to such stimuli is uneven among individuals. Following a customized evaluation on the intensity and salience of the stimuli in our brains, very few of these stimuli become the
targets of behavioral response. Recent studies on human behavioral response under social interaction extensively replicated the indispensable role of dopaminergic system and reward processing (Berridge and Robinson, 1998). For a long time, it has been thought that dopamine mediates the hedonistic feeling associated with receiving rewards (Skuze, 2009). However there is now accumulating evidence, which suggests that dopamine, does not mediate the hedonistic component (“liking”) but instead the motivational component (“wanting” or “incentive salience”) in rewarded behavior (Robinson et al., 2005). Many animal studies demonstrated deficits in predicting the stimuli as rewarding so to say “wanting” when the dopaminergic neurons are damaged experimentally (Robinson et al., 2005). Such dopaminergic activations related to “wanting” have a strong influence on cognitive faculties that facilitates the probability of approaching the predicted behavior, which was supposed to be rewarding (Barch, 2010). Notably, our motivational “wanting”, also depends on our metacognitive evaluations on the reward-predicting stimulus (Juckel et al., 2006; Takemura et al., 2011). Taken together, it is plausible to propose that, healthy behavioral approach to reward-predicting stimuli requires intact metacognitive capacities. Although the reward system is not the focus of this thesis, accumulating evidence defined the impact of the reward system on deficits in learning and motivation in schizophrenia (Simpson et al., 2012). Similar to the findings in healthy populations, schizophrenia patients did not present deficits in hedonic experiences (“liking”); such as their response to emotionally evocative positive stimuli (reviewed in Gold et al., 2008). Gold et al. (2008) conclude in their comprehensive review that, patients with schizophrenia present deficits in the ability to represent the value of outcome, and subsequently, required activation of the dopaminergic circuits were mostly unattended. Concerning the findings of the present thesis, in the absence of such motivated goal directed behavior under the influence of metacognition, it has been found that patients were not able to benefit from an experimental cognitive training (Study 1). In addition to that, perceived value of the training to improve WCST performance was under strong influence of metacognition. Taken together; metacognition in schizophrenia may play a supervisory role that acts on cognitive performance, by regulating intrinsic motivation and activating the necessary neurocognitive domains which are required to reach the goal directed behavior.

Some recent studies found that oxytocin administration increases affective components of theory of mind (Domes et al., 2007). Besides, there is well-replicated literature suggesting a positive correlation with emotion perception capacities and affective
ToM components in schizophrenia (i.e. Franklin et al., 2010). Apart from these findings, very little evidence supports the associations between endogenous oxytocin and high order social functioning in schizophrenia. Recently, Fischer-Shofty et al. (2013) conducted a study where they administer oxytocin before and after an interpersonal social performance task. They found specific but small effects of oxytocin on patients who lack social competence. Bartz et al. (2010) also replicated such finding in a study conducted in patients with autism. They observed improved empathy scores following oxytocin administration only in those patients who had more severe deficits in empathy. These studies provide sufficient evidence against the theories that suggest universal prosocial enhancement effects of oxytocinergic system. The authors concluded that, oxytocin may have increased the perceived salience of the stimuli, and hence was more effective when administered to participants who were less harmonized to social information yet had inappropriate judgments of social clues at baseline (Bartz et al., 2010). The finding on the specific effects of oxytocin only, in the emotion perception part of the social cognition training may partially support these explanations (Study 2). Taken together, it is plausible to argue that, although manipulating oxytocinergic activity may have beneficial effects on our patients, because these effects arise from the basic emotion and reward processing streams, observing direct translation of the effects to real life may be limited in behavioral studies conducted with schizophrenia patients.

Nowadays, oxytocin has become a target molecule to treat core social deficits in schizophrenia. The findings about the predictive role of oxytocin on emotion perception (Study 2) and its fine-tuning effects over the HPA axis (study 3) may be considered as preliminary evidence to support the Rosenfeld model in that extent. However, Rosenfeld pointed to the stress reducing effects of oxytocin, whereas the present thesis may suggest a fine-tuning effect, because, it has been found that an increased cortisol response was socially advantageous in patients who had higher oxytocin levels in study 3. Interestingly, patients’ cortisol response to stress, which was in relationship with oxytocin, has shown strong associations with subdomains of social functioning (study 3). Of equal interest, higher stress response, yet with better social functioning and social support has been demonstrated (study 3). Notably, “fine-tuning” was used as opposed to “stress buffering” because, although it is clear that external administration of oxytocin dampens the HPA axis, endogenous oxytocinergic systems may be activated only when the stress levels are higher than the individual can deal with. Alternatively, oxytocin may also sustain an appropriate HPA response during a social interaction that is appraised as stressful. Considering also the
The aforementioned effects of oxytocin on the amygdala and reward processing, it is plausible to argue that patients who found social interaction as more rewarding and prosocial (through activation in the oxytocinergic systems) showed appropriate stress responses that are necessary to maintain goal directed behavior. Though speculatively, one can also argue that the patients who had higher levels of cortisol reactivity (“normal cortisol response”), also present higher metacognitive capacities.

Notably, efforts to explore biological predictors of social functioning in schizophrenia did not give promising results in the past. However, study 3 highlighted cortisol reactivity to stress as a significant predictor, which was in close relationship with several subdomains of social functioning in schizophrenia. Interestingly, suppression of cortisol levels following dexamethasone has been assigned to numerous outcome parameters in early studies conducted in patients with depression and schizophrenia (i.e. Tandon et al., 1991). As it has been mentioned throughout this thesis, many studies concluded with an activation of cognitive faculties following an increase over the HPA axis yet under the influence of social (i.e. isolation) and psychological (i.e. mood, personality) factors. Taken together, it is plausible to argue that if cortisol response to social stress directly affects and is affected by social and cognitive factors, it may have more potential to be utilized as a biological outcome predictor in schizophrenia.

In light of these results, in addition to the traditional predictors such as symptom severity, neurocognition and social cognition in schizophrenia, biological response to stress and patient’s metacognitive capacity may be other components, which may contribute to how social behavior is driven in schizophrenia. Differently from the former ones, these two factors dynamically may form a beneficial behavioral response where the homeostasis is well kept. In general, such behavioral response may be in a spectrum between social withdrawal and engagement. Although, passive coping strategies such as social withdrawal and social avoidance are not beneficial for normal social functioning, they may still maintain the self's stability of homeostatic psychological equilibrium (Pollack et al., 1989) and thus improve life quality as described in Brenner et al. study (2009).

5.3. Limitations

5.3.1. Study 1

The first study has several limitations. Firstly, the impact of other neurocognitive confounders like sustained attention, which may have an influence on LP, were not taken into
account. This study does not reject the effects of neurocognitive faculties on individuals learning potential. It is clear that, patients with better attention and working memory capacity may have more potential to benefit from training. However, the main goal was to focus on other factors that contribute to learning potential. Secondly, the assessment of estimated IQ measured by MQ from the WMS-III is less common than other methods of estimated IQ evaluation. Thirdly, although the evaluation of perceived extrinsic motivation seems to have an acceptable face validity, further psychometric properties were not analyzed. Finally, to further elucidate the relationship between motivation and metacognition it may be more reliable to perform a structured intervention with multiple sessions, as compared to the experimental design used here. For example, intrinsic motivation and metacognition are potential domains to study for cognitive behavioral therapy programs in schizophrenia. Presumably, these domains may predict the treatment outcome of the patients who were involved in these programs.

5.3.2. Study 2

The main drawback of the second study is the small sample size. Therefore, the findings of this study require replication in larger samples. Secondly, the hypothesis of Study 2 was based on the effects of basal oxytocin levels, hence the oxytocin levels were only measured at baseline. However, post-training levels of oxytocin could also be informative to comment on causal role of dynamic oxytocinergic changes over social cognition domains. Moreover, a study where intranasal oxytocin was administered during the training would be informative in terms of domain specific effects of oxytocin (i.e. Pedersen et al., 2011). Lastly, neurocognitive domains such as attention and executive functioning are important predictors of treatment outcome in schizophrenia. Data on these domains were not collected in this study, thus the effects of these domains over treatment outcome and oxytocin levels could not be ruled out. Lastly, metacognition and motivation appeared to be crucial predictors on cognitive remediation in Study 1. However, the roles of these domains were not ruled out in this study.

5.3.3. Study 3

The third study has several limitations. Firstly, there is a debate on the use of a median-split approach in the literature (MacCallum et al., 2002). However the use of this approach is legitimate in such cases when the categorized variables represent two different
types within the observed sample, like our case (i.e. cortisol responders vs. non-responders) (Maccallum et al., 2002). Besides, multivariate analyses further supported the univariate findings in this study. Secondly, although the results were consistent, several univariate analyses were conducted without correction for multiple comparisons, thus increasing type I errors. Nevertheless, since examination of the relationship between cortisol reactivity, social functioning and social support is still exploratory, conservative solutions such as Bonferroni correction may tend to be overly stringent in such cases (Perneger, 1998). Lastly, although the results of this thesis are potentially relevant for the development of future treatment strategies for schizophrenia, it is not clear as to whether or not the relationship between oxytocin and cortisol found in this study is specific to schizophrenia. The lack of a control group is one important problem, which had restrained the study to make firm conclusions.

5.4. Open Questions

Despite the evidence coming from ample of studies on the causes of social dysfunction in schizophrenia, our knowledge on this topic is still immature. However, with the contribution of neuroscience in the last decade, we now have more room to understand how schizophrenia occurs. In addition, such an increase in the quantity of previous studies created a large heap of information that is waiting to be harvested. Taken together, this area requires more of an integration between clinical and cognitive neuroscience.

Regarding the first study, if metacognition and motivation can explain learning potential and social functioning up to some degree, than current psychosocial therapies might consider implementing techniques, which aim to improve these domains. In the literature, as far as known, there is one integrated metacognition training (MCT, Moritz and Woodward, 2007) and one social cognition training (SCIT, Roberts and Penn, 2009) that demonstrated promising and well-replicated results in schizophrenia. However, the predictors of treatment outcome for these interventions have not been studied yet. Nonetheless, as mentioned previously, Kurtz et al. (2011) launched a meta-analysis on social cognition interventions, but his study provided limited conclusions in regards to the moderator role of previous social cognitive and neurocognitive domains on treatment outcome. Besides, metacognitive training was not interest of Kurtz et al study. Considering, the heterogeneous characteristic of schizophrenia patients, individual psychological interventions based on patient’s metacognitive capacity, motivation and learning potential would become potential are of
interests in schizophrenia research. In addition to these cognitive factors, biological factors such as oxytocin may be used as biomarkers to develop individualized treatments in schizophrenia. Some of these biological predictors may also serve for treatment purposes. For example, considering the findings of this thesis, patients with higher oxytocin levels may be more likely to benefit from emotion perception training. Alternatively, patients with lower levels oxytocin may benefit from oxytocin administration throughout the training as an augmentation therapy in addition to their conventional antipsychotic treatments.

Concerning cortisol reactivity to stress in schizophrenia and the role of oxytocin, the third study provides important insights. However, to confirm the finding on fine-tuning effects of oxytocin, a study where social anxious individuals compared with schizophrenia patients would be utmost interesting. Nevertheless, in-group differences and correlations suggest the utilization of cortisol reactivity as a predictor of social functioning in schizophrenia. As a note of caution, the sample of the present thesis was consisting of clinically stable patients and so, these findings need replication in different illness stages of schizophrenia. Furthermore, efforts on exploring the effects of oxytocin administration on cortisol reactivity in schizophrenia could enlighten their causal relationship. However, in light of the aforementioned data, such work may consider to account for the plasma oxytocin levels before observing the stress buffering or tuning effects of oxytocin administration.

Interestingly, cortisol response to stress may also relate to patients’ impaired metacognitive abilities. Specifically, patients with higher self-reflectivity and decentration capacities may demonstrate an appropriate cortisol response to stress, which is necessary to cope with the environmental stimuli in schizophrenia. In addition, future studies should also focus on the effects of social milieu on metacognition, oxytocin, and our biological stress coping mechanisms in schizophrenia. I believe that understanding the interconnections between these domains would ultimately impact on developing new treatment strategies on the way to attain social recovery in schizophrenia.

Although not the focus of this thesis, whether or not neuronal activity in the reward processing is related with behavioral measures of motivation and metacognition should be the interest of future work. In the last couple of years, fMRI studies demonstrated the reward related areas in the brain that appear to be less active in patients with schizophrenia. However, clinical translations of these findings are still at the speculative level. Furthermore, although social cognition domains such as theory of mind, emotion perception, and social perception are well studied with fMRI, we are not aware of any neuroimaging work that
proposes enlightening the brain network related to metacognition in schizophrenia. Nevertheless, few studies investigated the network activity in metacognition with functional connectivity techniques, and provided remarkable results in healthy participants. Regarding the methodology, current neuroimaging statistical techniques are limited in exploring such behavioral responses with activations in the brain, because these techniques were at first designated to map the cognition related areas. However, recent efforts with computational methods and permutation-based analyses appear to be the potential techniques to explore causal relations between behavior and brain activity in the future.
CHAPTER 6

"There may not be a magic bullet for schizophrenia,"

Thomas Insel

CONCLUSIONS

Schizophrenia has diverse clinical expressions, which reflects numerous etiological factors, such as variations of the neurotransmitter systems, receptor polymorphisms, differences in the parental care, deviations in the behavioral and biological stress coping mechanisms, social, and neurocognitive developmental delays, traumatic experiences and personality traits. Therefore, it is unlikely that future studies would bring up a single hypothesis that can explain all known faces of schizophrenia. Instead, developing unified theories would allow us to come up with novel treatment strategies to help our patients to improve their social functioning and facilitate their reintegration to society.

Taken as a whole, the present work hopefully adds to develop a more integrative approach to the understanding of social functioning in schizophrenia, taking into consideration the pathway between neurobiology and behavior. I believe that such integrative approaches that bridge the neuroscientific findings with the clinical results will be the future trend in schizophrenia research.
REFERENCES


Bell, M.D., Mishara, A.L., 2006. Does negative symptom change relate to neurocognitive change in schizophrenia? Implications for targeted treatments. Schizophr Res 81, 17-27.


REFERENCES


Harvey, P.D., Penn, D., 2010. Social cognition: the key factor predicting social outcome in people with schizophrenia? Psychiatry (Edgmont) 7, 41-44.


Kreifelts, B., Ethofer, T., Huberle, E., Grodd, W., Wildgruber, D., 2010. Association of trait emotional intelligence and individual fMRI-activation patterns during the perception of social signals from voice and face. Hum Brain Mapp 31, 979-991.


LeBlanc, J., Ducharme, M.B., Thompson, M., 2004. Study on the correlation of the autonomic nervous system responses to a stressor of high discomfort with personality traits. Physiol Behav 82, 647-652.


REFERENCES


REFERENCES


Sergi, M.J., Kern, R.S., Mintz, J., Green, M.F., 2005. Learning potential and the prediction of work skill acquisition in schizophrenia. Schizophr Bull 31, 67-72.


REFERENCES


Curriculum vitae

Cumhur TAS, MD
International Graduate School of Neuroscience
LWL University Hospital; Ruhr-University of Bochum.
Alexandrinenstr. 1, D-44791
Bochum, Germany.
Phone: +49-234-5077-1220
fax: +49-234-5077-1119
e-mail: cumhur.tas@rub.de

PERSONAL DATA:

Place and Date of Birth: Ankara, 29/10/1981
Nationality: Republic of Turkey
Family status: Married
Languages: English (C1)
German (B2)
Turkish (Native)

EDUCATION:

Pre-Medical Degree: Adnan Menderes University, Faculty of Medicine, Aydin, Turkey, 1999-2002.
Medical Doctor Degree: Adnan Menderes University, Faculty of Medicine, Aydin, Turkey, 1999-2005.
Residency in Psychiatry: Celal Bayar University, Faculty of Medicine, Department of Psychiatry, Manisa, Turkey, 2006-2011.
Clinical Research Associate: King’s Collage, Institute of Psychiatry, London, UK, 2008-2009 (Honorary Contract)
PhD in Neuroscience: Ruhr University, International Graduate School of Neuroscience, Bochum, Germany, 2010-2013 (expected).
**Doctor of Medicine (M.D)**  
Republic of Turkey Ministry of Health, General Directorate of Personnel, Ministry of Education and Specialization, Specialization Branch Registration Number: 2005-3-5-8306  
Registration Date: 06.01.2005

**Specialist in Psychiatry (PhD-Fachaertz)**  
Republic of Turkey Ministry of Health, General Directorate of Personnel, Ministry of Education and Specialization, Specialization Branch Registration Number: 91316  
Registration Date: 16.06.2011

**Dissertation Thesis:**  
*Psychiatry, Celal Bayar University, Izmir, Turkey*  

---

**REPORT OF EVALUATION OF EDUCATIONAL CREDENTIALS:**

**Certificate for Computerized Cognitive Remediation in Psychosis**  
King’s Collage Institute of Psychiatry, UK, 2009.

**Certificate for Cognitive Behavioral Therapy,**  
CBT@GP Association 18 hours theoretical training. Malatya, 2010. Compos Mentis 40 hours theoretical training. Turkey, 2006.

**Certificated SPSS Course- Statistics**  

**Social Cognition and Interaction training in Schizophrenia**  

**Certificated SPM (Statistical Parametric Images) – fMRI(functional MRI)and VBM (Voxel Based Morphometry) course (Brain imaging**
CIRCUUM VITAE

Certificated advanced course on statistics:

Research School, Ruhr University, Bochum, Germany, 2011.

Certificated research proposal preparation course:

Research School, Ruhr University, Bochum, Germany, 2011.

Workshop - Evidence Based Medicine in Psychotic Disorder

Lundbeck Institute, Copenhagen, Denmark, 2008.

PROFESSIONAL WORKING EXPERIENCE:

2005-2006 General Practitioner Saydam Medical Center Kusadasi, Turkey
2006-2011 Residency in Psychiatry Celal Bayar University, Faculty of Medicine, Department of Psychiatry, Izmir, Turkey
2008-2009 Clinical Research Associate King’s Collage Institute of Psychiatry (Psychology Dep. 2008-2012 (Honorary Contract)
2011 Research Assistant, Ph.D. Candidate Research Department of Cognitive Neuropsychiatry and Psychiatric Preventive Medicine, Department of Psychiatry, LWL University Hospital, Ruhr-University Bochum, Germany

HONORS & AWARDS:

2005: Turkish Schizophrenia Federation: Best Psychosocial Rehabilitation project in Schizophrenia Award
2010: Ruhr University, PhD Scholarship.
2011: Ruhr University, Acceptance for research school for
2012: Publication Award - Scientific and Technological Research Council of Turkey (TUBITAK) (Tas et al., 2012,
CIRCUlUM VITAE

Psychiatry Research)

PROFESSIONAL AND NONPROFESSIONAL ORGANIZATIONS:
2005 Turkish Medical Association
2006 Turkish Psychiatry Association, Local Manisa Secretary
2006 Turkish Psychiatry Association, Psychiatric Rehabilitation Unit Member
2007 Psychiatry Association, Schizophrenia Unit Member
2007 Manisa, Life With Schizophrenia Association- council member
2011 Schizophrenia International Research Society member

FIELD OF INTEREST
Schizophrenia, Social cognition, Social functioning, Neurocognition, Neuroimaging

AD HOC REVIEWER
Psychiatry Research-2012
European Psychiatry-2012
Schizophrenia Research and Treatment-2012
Comprehensive Psychiatry-2012
LIST OF PUBLICATIONS

- **Published Journal Articles:**


- Other published articles:


- Journal Articles submitted:


- Articles in preparation:


- **Book chapters (contract approved)**


- **Refereed Conference Papers, Seminars and Published Abstracts:**

21. Danaci A.E, Gulseren L, **Tas C.**, Cubukcuoglu Z. Factors that affect the perceived family burden of the families which has a schizophrenic member, 11 th Spring Symposium of Turkish Psychiatry Association, Turkey, 2007.

22. **Tas C.**, Interventions to improve social cognition in schizophrenia: Review 45th National Congress of Turkish Psychiatry Association, Turkey, 2009.


25. **Tas C.**, Neurocognitive improvements in psychosocial interventions in schizophrenia, 47 th National Congress of Turkish Psychiatry Association, Turkey, 2011.


Acknowledgements

I would like to express my deepest gratefulness to all those who provided me the possibility to complete this work:

First, I would like to thank to the patients who have participated to these aforementioned studies. Without their contribution, it is clear that I would not be able to prepare this report.

I would like to thank to Cristina Gonzales, Duygu Kuzu, Orkun Aydın, Kadir Aşçıbaşı, Eva Shweer and Jasmin Salihy for their help in collecting data and contributing to the drafts of the manuscripts and this thesis.

I would like to give my special gratitude to:

My supervisor, Prof. Dr. Martin Brüne, whose contribution with thoughtful suggestions and encouragement helped me a lot not only in conducting these projects and preparing this report but also in developing myself as researcher, clinician, father and human being. I take his humility and leadership as a “life lesson” during the time that I stayed in Ruhr University. Ich bedanke mich vielmals.

Prof. Dr. Oliver T. Wolf for being my second supervisor, and providing suggestions on my first study, which helped me a lot to develop my experiment.

Prof. Dr. Aysen Esen-Danaci for being my collaborator and providing access to patients in Turkey.

Elliot Brown for walking together during the PhD time. I should state that, without his contribution, I could not find the courage to complete all the academic activities that you have seen in my CV. I have never had such a great colleague in my life, and probably will not also have in the future. For me he is not only my colleague, because before coming to Bochum, I only had a sister, but now I believe that I have a new brother.

My wife and my son, Zeynep and Cem for spending these three years with me in Germany. We had dozens of problems, which we together got over successfully every time. Without you, this work could not be finished. I love you...

My mother, father and sister for being there whenever I need…
Last words go to someone who I will meet 8 months later. You have not seen me while I wrote this thesis. But, believe me that this work has progressed a lot after I have heard you coming from your mother...