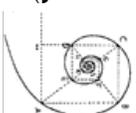




Università degli Studi di Milano
Dottorato in Medicina Molecolare e Traslationale



TESI DI DOTTORATO

Ciclo XXIX

Anno Accademico 2015/2016

Bruno BIAGIANTI

Dottorando: Bruno BIAGIANTI

**Investigating the neurophysiological effects of
oxytocin administration on healthy subjects
and individuals with schizophrenia spectrum
disorders using Magnetoencephalography
Imaging (MEG-I).**

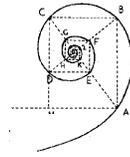
Tutore: Prof. Orsola GAMBINI

Coordinatore del Dottorato Ch.mo Prof. Mario Clerici

CICLO XXIX



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TESI DI DOTTORATO DI RICERCA

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Investigating the neurophysiological effects of oxytocin administration on healthy subjects and individuals with schizophrenia spectrum disorders using Magnetoencephalography Imaging (MEG-I).

Dottorando : Bruno BIAGIANTI

Matricola N°R10707

TUTORE : Prof.sa Orsola GAMBINI

COORDINATORE DEL DOTTORATO: Ch.mo Prof. Mario CLERICI

Abstract

INTRODUCTION Schizophrenia-spectrum disorders (SZ) are characterized by disturbances of early information processing across various sensory modalities that originate from disrupted spatial and temporal linkage in critical neural networks that include the limbic system and sensory cortices. These disturbances are known to underlie impairments in social cognition, i.e. the ability to understand the thoughts and behaviors of others, which is a critical skill for effectively navigating the social world. Patients with SZ have widespread social cognitive deficits that interfere with social relationships and impair occupational functioning. Current pharmacological treatments are ineffective in remediating social cognitive deficits and in regulating their neurophysiological underpinnings. The oxytocin (OT) system, which is critically involved in social behavior and cognition in mammals and is dysregulated in SZ, is a promising target. Intranasal administration of exogenous OT is well tolerated and improves social cognition in patients with SZ. Additionally, neuroimaging studies in healthy individuals suggest that OT improves information processing and social cognition by modulating regional activity within those neural networks that are impaired in SZ. While work on healthy individuals is promising, no studies investigated the effects induced by OT on spatiotemporal neural oscillatory patterns in patients with SZ.

MATERIAL & METHODS. In this study, I used Magnetoencephalography Imaging (MEG-I) to examine the effects of OT. I administered a single intranasal dose of OT (40 IU) or placebo (PL) in a randomized, double-blind, counterbalanced order with a cross-over, within-subject design to 25 males with SZ and 25 matched healthy controls (HC). Participants' brain activity was recorded using MEG-I while they completed an auditory deviance task and a facial emotion processing task that robustly activate neural networks underlying information processing and social cognition. Change in auditory mismatch negativity induced by OT/PL in SZ and HC was assessed repeated measures ANOVA. Induced oscillatory activity in regions displaying early activation patterns was examined using adaptive spatial filtering techniques. Broadband activity estimated at each time point in a trial was averaged across trials, root-mean-square transformed, and z-normalized. Average amplitude from early time windows post-stimulus onset was calculated to assess early responses in the bilateral occipital face area (OFA) and the right amygdala. The Neurodynamic Utility Toolbox for MEG-I was used to conduct an exploratory time-frequency analysis of the neural sources during the processing of facial emotions. Task-induced neural oscillatory power changes were localized and examined after OT and PL administration.

RESULTS. Compared to HC, SZ showed reduced amplitude of the mismatch negativity under PL. This impairment was normalized after OT administration. Under the effects of PL, the exploratory time-frequency analysis found differential early activations in SZ subjects relative to HC in several regions of interest, including the bilateral OFA and the right amygdala. In the OFA, SZ subjects showed impaired M100 responses that were normalized by OT, while HC showed no effects of OT on M100 response. In the right amygdala, SZ showed aberrant theta activity and impaired M100 under PL. These responses were normalized by OT.

CONCLUSION. MEG-I analysis provided detailed measures of the location and time course of neural activations induced by OT. In SZ, OT remediated impaired facial emotion processing and auditory deviance processing, by normalizing the aberrant underlying early activation patterns. Future analyses will examine the neurophysiological effects of OT on late activation patterns in associative and cognitive control areas. This knowledge is critical to optimizing the use of OT as a treatment for social cognitive impairments in SZ and other neuropsychiatric illnesses.

Sommario

INTRODUZIONE I disturbi dello spettro schizofrenico (SZ) sono caratterizzati da alterazioni della elaborazione precoce di informazioni in diverse modalità sensoriali che origina da disconnessioni spaziali e temporali nei circuiti neurali che includono il sistema limbico e le cortecce sensoriali. Queste alterazioni rappresentano le basi dei deficits di cognitiv  sociale, cio  la capacit  di comprendere pensieri e comportamenti altrui, una funzione critica per un buon funzionamento sociale. I pazienti con SZ hanno diffuse deficits della cognitiv  sociale che interferiscono con le relazioni interpersonali e debilitano il funzionamento occupazionale. I trattamenti farmacologici attualmente disponibili non sono efficaci nel trattare i deficits di cognitiv  sociale e nel regolarne i substrati neurofisiologici. Il sistema dell'ossitocina (OT), che   significativamente coinvolto nella cognitiv  e comportamenti sociali nei mammiferi ed   sregolato in SZ,   un target promettente. La somministrazione intra-nasale di OT   ben tollerata e migliora la cognitiv  sociale in pazienti con SZ. Inoltre, studi di neuro-imaging in soggetti sani suggeriscono che OT migliora l'elaborazione di informazioni e la cognitiv  sociale tramite la modulazione di attivit  regionale nei network neurali che sono alterati in SZ. Mentre i risultati in soggetti sani sono promettenti, non esistono attualmente progetti che hanno studiato gli effetti indotti da OT sui patterns spatio-temporale di oscillazione neurale in pazienti con SZ.

MATERIALI E METODI In questo studio, ho usato la Magnetoencefalografia (MEG-I) per esaminare gli effetti di OT. Ho somministrato una singola dose intra-nasale di OT (40 UI) o placebo (PL) in un studio randomizzato, doppio-cieco, a ordine controbilanciato con cross-over within-subject design a 25 soggetti maschi con SZ e 25 soggetti sani (HC). L'attivit  cerebrale dei partecipanti   stata registrata con MEG-I durante un test di devianza uditiva e un test di riconoscimento di emozioni facciali che attivano in maniera robusta i network neurali alla base dell'elaborazione di informazioni e della cognitiv  sociale. Cambiamenti nella auditory mismatch negativity indotti da OT/PL in SZ e HC sono stati misurati con ANOVA per prove ripetute. Attivit  oscillatoria indotta in regioni con patterns di attivazione precoce   stata esaminata usando tecniche di filtraggio spaziale adattivo. Per l'attivit  a banda larga stimata per ogni punto temporale   stata calcolata la media tra i trials, trasformata in scarto quadratico medio, e z-normalizzata. La ampiezza media dalle finestre temporali precoci dopo la presentazione dello stimolo   stata calcolata per valutare risposte precoci nella area facciale occipitale (OFA) bilaterale e nell'amigdala destra. Ho usato il Neurodynamic Utility Toolbox for MEG-I per condurre una analisi tempo-frequenza esplorativa della sorgenti neurali durante l'elaborazione di emozioni facciali. I cambiamenti nel potere neurale oscillatorio indotti dal task sono stati localizzati ed esaminati dopo la somministrazione di OT e placebo.

RISULTATI. In contrasto con i HC, SZ hanno mostrato una ridotta ampiezza della mismatch negativity durante il placebo. Questo deficit   stato normalizzato dopo la somministrazione di OT. Durante il placebo, l'analisi tempo-frequenza esplorativa ha trovato diverse attivazioni precoci differenziali nei soggetti con SZ rispetto ai HC in diverse regioni di interesse, incluse la OFA bilaterale e l'amigdala destra. Nella OFA, i soggetti con SZ hanno mostrato deficits della risposta M100 che sono stati normalizzati da OT, mentre i HC non hanno mostrato effetti di OT sulla risposta M100. Nell'amigdala di destra, i soggetti con SZ hanno mostrato attivit  teta aberrante e risposta M100 deficitaria durante il placebo. Queste risposte sono state normalizzate da OT.

CONCLUSIONI. L'analisi MEG-I ha fornito misure dettagliate della localizzazione temporale e spaziale delle attivazioni neurali indotte da OT. In SZ, OT ha corretto i deficits nell'elaborazione di emozioni facciali e della devianza uditiva, normalizzando i patterns aberranti di attivazione neurale precoce. Analisi successive esamineranno gli effetti neurofisiologici di OT sui patterns di attivazione tardive in aree associative e di controllo cognitive. Questa conoscenza   necessaria per ottimizzare l'uso di OT come un trattamento per i deficits di cognitiv  sociale in SZ e in altri disturbi neuropsichiatrici.

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1. INTRODUCTION

1.1. *Schizophrenia spectrum disorders: faulty sensory processing and integration*

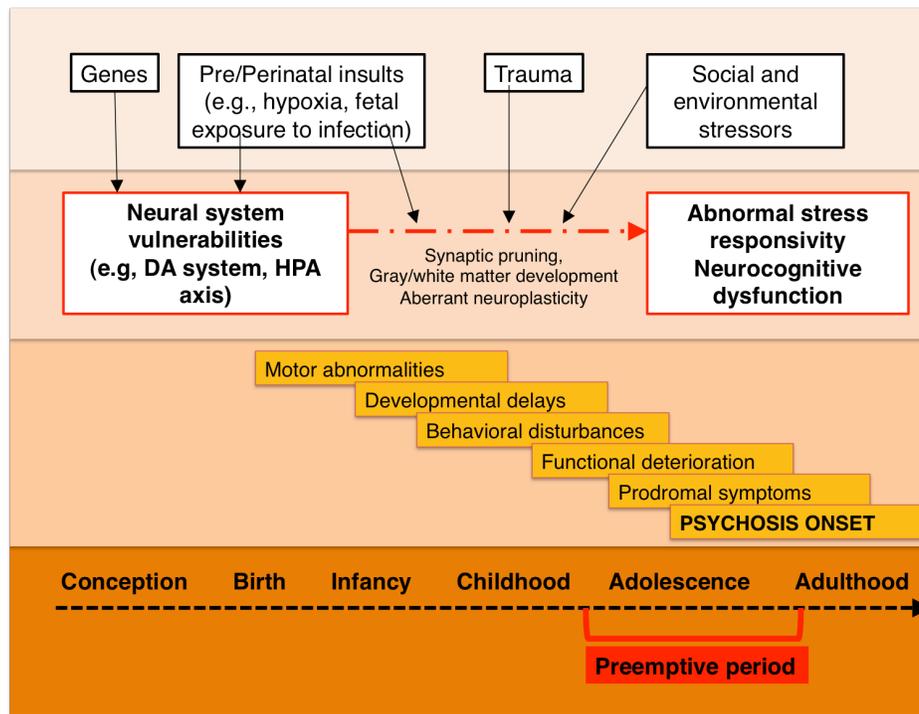
1.1.1. **A neurodevelopmental model for schizophrenia spectrum disorders**

Schizophrenia is a serious psychiatric illness that affects approximately 51 million people worldwide and has direct and indirect medical costs that exceed those for depression, dementia, and other medical illnesses across most of the lifespan[1]. Despite the development of evidence-based treatments, it remains one of the leading causes of life long disability. Currently, evidence-based recommendations for the treatment of schizophrenia suggest a combination of psychopharmacological and psychological intervention. Although many effective treatments exist, their impact remains limited: real-world functioning and quality of life of individuals struggling with schizophrenia has remained essentially unchanged for the past half century[2].

Schizophrenia is characterized by hallucinations, delusions, disorganized behavior, cognitive impairments, and poor psychosocial outcomes. Genetic liability factors interact with environmental insults, many of them occurring during the pre- and perinatal period, with the result that at-risk individuals are vulnerable to a range of environmental stressors. This interaction of genes and environment leads to aberrations in brain development and neural network functioning, which are not typically evident until adolescence or very early adulthood, when brain maturation is nearing completion[3, 4].

At that point, usually as a response to environmental stressors, the individual (who may until then have had no observable symptoms or only mild nonspecific symptoms), experiences “psychosis,” or a break with reality, often initially in mild or attenuated form, which - if left untreated - then progress into a full-blown psychotic episode. Schizophrenia must thus be understood as a neurodevelopmental neurocognitive disorder characterized by decreased efficiency and abnormal connectivity in cortical and subcortical neural networks, rendering young individuals particularly vulnerable to the deleterious effects of stress.

Figure 1. A stress-vulnerability model for schizophrenia



Few new breakthroughs in identifying and treating the neurobehavioral and cognitive mechanisms that result in psychosis have been made in recent decades. This lack of progress is due, in part, to the scientific focus on studies of individuals who meet criteria for heterogeneous, categorical diagnoses in comparison to control subjects who are often atypical in their “normalcy.” Psychotic symptoms are characteristic of schizophrenia spectrum disorders, but are also observed in other disorders, including bipolar disorder, depression with psychotic features, post-traumatic stress disorder and obsessive-compulsive disorder, and thus lack diagnostic specificity.

For these reasons, the National Institute of Mental Health (NIMH) has operationalized Research Domain Criteria (RDoC) approach to understand psychosis. The RDoC approach was developed to provide a framework for conducting research that is focused on a narrow clinical problem which may cut across conventional diagnostic boundaries and that can be studied along a dimension from healthy to various severity levels of pathological. The RDoC approach encourages recruitment of study participants who span a range from intact to gradations of impairment on the dimension(s) of interest, independent of diagnosis.

The RDOC framework explicitly states that “while the hypotheses and supporting data may be generated in a specific diagnostic group, the study design should be independent of a specific clinical diagnostic category. Recruitment and eligibility would generally not be determined on the basis

of diagnostic category, but would instead be based on criteria that would result in a sample that is optimized to study the narrowly-defined clinical problem and RDoC construct(s) of interest. RDoC's emphasis on understanding the full dimensionality of neurobehavioral functioning generally precludes dichotomous "patient versus controls" analyses, but if, after examining the characteristics of the dimension(s) of interest, discontinuities or tipping points are detected, between-groups analyses are justifiable".

Following these guidelines, I first identified the dimension of interest – psychosis – and the RDoC construct –information processing. As the eligibility criteria of the project were not supposed to reflect a diagnostic category (the DSM IV-TR diagnosis of schizophrenia) but the dimensionality of psychosis, which several authors referred to as the “schizophrenia spectrum”, I recruited a diversified and representative sample of patients with the diagnoses of schizophrenia, schizoaffective or bipolar disorder with psychotic features. This is in line with several studies referenced in this dissertation. For the sake of readability and simplicity, I will consistently refer to subjects recruited for the study as patients with schizophrenia spectrum disorders (SZ), although it is necessary to note that the psychopathological features of psychosis may vary among schizophrenia, schizoaffective and bipolar disorder with psychotic features. Limitations of this approach are presented in the discussion chapter of this thesis. Similarly, the RDOC framework highlights that individuals who are experiencing symptoms of psychosis but have not yet engaged in treatment (2 in our sample) provide an opportunity to study to test novel hypotheses about response to pharmacological agents, including oxytocin.

Additionally, in this experiment I chose two constructs –sensory processing and facial emotion processing—that are specifically related to psychosis as they are to other aspects of psychopathology (like autism and social anxiety disorders). Nonetheless, the constructs are invoked in many of the prominent models of psychotic symptoms, thereby providing a strong theoretical and empirical background for the experiments described in this dissertation. Although the structure of the RDoC matrix suggests boundaries among constructs, given the densely integrated and interconnected nature of the brain's circuits, it is understood that the constructs function interactively and that promising empirical approaches to treating individuals with psychotic disorders may involve examining intersections among constructs.

1.1.2. Disturbances of the sense of self in schizophrenia spectrum disorders

The schizophrenia spectrum has been described as a psychiatric condition associated with the loss of a coherent sense of “self”. For pragmatic reasons we describe here the “normal” sense of self as a feeling of unitary entity, the “I”, that owns and authors its thoughts, emotions, body and actions. The ‘basic’ self is, in other words, a pre-reflective, tacit level of selfhood. Like our nose is always present in the center of our visual field, a ‘background composition of multisensory input’, responsible for an

abstract awareness of ourselves, is present in every experience we have. This 'sensory self' is analogous to phenomenological concepts as 'presence', 'core self', 'minimal self' or 'ipseity'[5].

Disturbances of the self impair the processes of self-recognition and self-other discrimination. Examples of these disturbances include reduced recognition of the body, impaired emotion processing, abated authorship, and impaired source discrimination[6–9]. Basic self-disturbances occur in all following stages of schizophrenia can be observed independently of symptoms throughout large periods of the course of illness, are present in non-psychotic family members of schizophrenia spectrum patients, and distinguish schizophrenia spectrum conditions from other psychoses[10, 11].

Insights from phenomenological psychiatry and philosophy, focused on disturbed subjectivity, indicate that disturbed self-experience or selfhood may underlie the sub-delusional detachment from reality that often precedes the onset of psychosis, and generate many "surface-level" psychotic symptoms, particularly in schizophrenia spectrum disorders, including hallucinatory experiences, delusional detachment from reality, diminished sense of presence, depersonalization, blurred boundaries[5].

1.1.3. The sense of self and sensory processing

In order to develop a normal sense of self, the ability to process and integrate multisensory input is essential[12, 13]. Although multisensory input from the environment continuously informs us, which is essential for normal self-experience[14], we are nonetheless demarcated from it[15]. The neurobiological process of organizing, processing and integrating sensory information is therefore crucial to establish effective interaction within the environment.

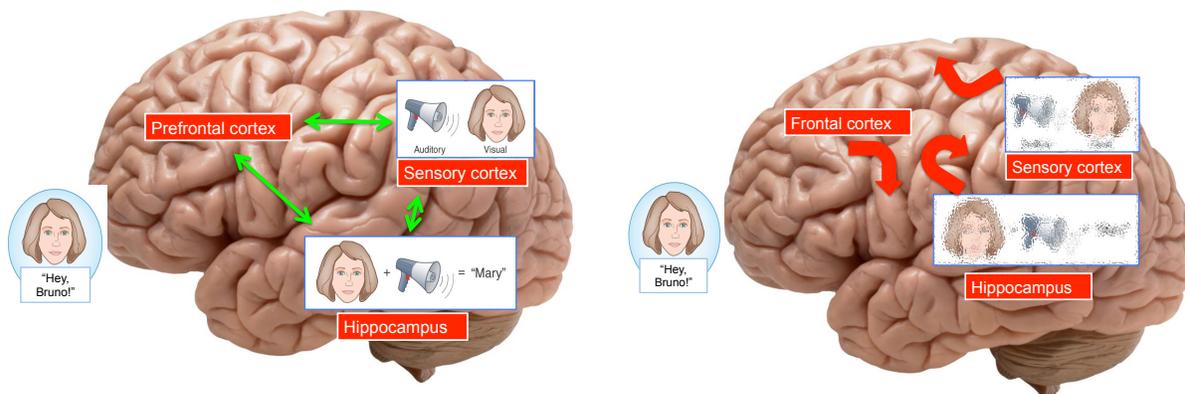
Disturbance of self in schizophrenia spectrum disorders has been linked with dysfunction in sensory processing and integration[16]. Briefly, if multisensory information processing and integration is aberrant, the formation of the sense of self and the demarcation between the self and the environment can become problematic. Having difficulty organizing sensory stimulation from the surrounding environment is logically paralleled by difficulty in mounting an appropriate response when necessary. An example of disturbances in early sensory processing and integration could help clarify the aforementioned concepts.

Let's suppose that I run into a dear friend of mine, Maria, while walking on the streets. My brain undergoes a well coordinated sequence of neural activations. First of all, the prefrontal cortex is in a preparatory state that permits to predict sensory information inputs. The sensory cortices perceive within sensory signals, in this example Maria's face and Maria's voice. The frontal cortex focuses attention on these signals, filters out irrelevant information, including distractors, background noise or other peripheral visual elements. Finally, rapid comparisons and predictions are made by retrieving

memory information about Maria from the hippocampus. This happens incredibly fast, for any sensory modality, probably in less than 200 ms. The process is automatic, pre-attentive, and very efficient, so that I can start my conversation with Maria almost effortlessly.

In patients with schizophrenia spectrum disorders, impairments are present at every stage of this process. First of all, the encoding of Maria's face and voice is very noisy and imprecise. Additionally, the frontal cortex has enormous difficulties in focusing attention, in holding this noisy information on line, and in filtering out irrelevant information. Finally, the memory systems of the hippocampus are also impaired, so it's impossible to retrieve useful information. This results in the inability to easily and rapidly recognize Maria and engage with her in a conversation. If we extend this example to every single environmental input to which we are normally exposed, we can imagine the challenges that individuals with schizophrenia spectrum disorders encounter, as well as some of the perceptual and cognitive distortions that characterize them clinically.

Figure 2. Early sensory processing in healthy individuals and patients with schizophrenia spectrum disorders



Many authors have attempted to link some of the basic self disturbances commonly found in schizophrenia spectrum disorders with findings of faulty multisensory processing. Subjective reports ranging from visual and auditory distortions to vivid hallucinations are paralleled by deficits in auditory and visual processing. Visual psychophysical measures have documented deficits affecting motion perception[17], form perception[18], low spatial frequency discrimination[19], location discrimination[18], and backward masking performance[20]. Within the auditory domain, patients with schizophrenia spectrum disorders exhibit deficits on behavioral measures of tone matching, temporal

discrimination, and pitch discrimination[21, 22]. Similarly, the basic self disturbance of 'diminished presence' may result from deficits in somatosensory feedback, which undermine the perceived sensory self. Similarly, difficulties with self-other discrimination could originate from disturbances of haptic sense of proprioception. In fact, proprioception and tactile sensations are essential for sense of action and boundaries, and individuals with schizophrenia spectrum disorders are known to have reduced haptic sense and proprioception[23, 24] which could lead to reduced boundary recognition[25]. In turn, reduced boundary recognition could compromise discrimination between internal and external sensory inputs, a process that is necessary for self-other discrimination. Reduced source discrimination (e.g. misattribution of own actions to others) could therefore be the result of reduced boundary recognition[26]. Impaired self-monitoring and source monitoring have been found to correlate with auditory hallucinations, thought intrusion and alien control symptoms[24, 27] In sum, depending on which somatosensory feedback is impaired, sensory processing abnormalities may cause depersonalization, blurred boundaries, cenesthopathies and/or diminished sense of ownership and agency.

1.1.4. Studying sensory processing in schizophrenia spectrum disorders

The high complexity of early sensory information processing does not only involve sensory brain regions simply relaying neural representations of the environment to higher order networks, but also requires that incoming information is preconsciously filtered and digested via top-down and bottom-up loops[28].

In focusing on sensory dysfunction as a potential etiological factor, neurophysiological research in the recent decades has studied early sensory processing in schizophrenia spectrum disorders using encephalographic techniques or functional magnetic resonance imaging, that permit objective evaluation of neural responses that occur early in time following delivery of a sensory stimulus (generally within the first 100–200 ms).

Techniques like Magnetoencephalography (MEG) and eletroencephalography (EEG) record electromagnetic fields (measured by sensors outside the head) that are produced by electrical activity within the cortex. Because EEG/MEG provide a direct measure of electrical activity within the brain, with a very high temporal resolution (milliseconds), and is an excellent technique of assessing early neural operations as individuals encode and process information arising from environmental stimuli.

Functional Magnetic Resonance Imaging (fMRI) provides an indirect measure of neural activity through detection of changes in blood flow. Because fMRI provides much better spatial resolution (sub-millimeter thresholds), compared to EEG/MEG recordings, it is optimal for detection of neural activation in higher-order regions of the brain during more complex cognitive operations.

Dysfunction in the coordination of neural activity at the earliest stages of sensory processing is now known to be a core feature of schizophrenia spectrum disorders: several studies have demonstrated that patients with schizophrenia spectrum disorders are significantly impaired even in routine processing of simple stimuli[29–31]. This wide spectrum of sensory processing abnormalities is present early in the course of the illness, and precedes the emergence of psychotic symptoms[32–34]. Impairments in early sensory processing have been well documented in the schizophrenia spectrum for every sensory domain (visual, somatosensory, interoceptive, pain and olfactory systems)[35]. Fundamental sensory processing abnormalities, including de- and en-coding of information, sensory gating, backward masking, etc., are known to lead to aberrant neurocognitive-perceptive processes that result not only in basic self disturbances, but also in inattentiveness, disorganization and symptoms that cause significant disruption in real world functioning[36]. Finally, it has also been argued that impairments in basic sensory processing abilities may determine poor social functioning[37].

Table 1. Multi sensory disturbances in the schizophrenia spectrum (from Postmes et al., Schizophrenia Research, 2014)

Senses	Sensory deficit	Senses	Sensory deficit
Olfactory sense	Deviant olfactory experiences		Visuo-vestibular disintegration Caloric vestibular nerve stimulation is beneficial
Haptic sense	Olfactory functions, meta-analysis Structural impairments olfactory system Sensitivity and processing Altered self/other discrimination Higher susceptibility for Rubber Hand Illusion	Interoception	Autonomic abn. & disconnection response Simult. co-activation two evaluative systems Interoception related to emotion processing Pain processing and monitoring
Propriocepsis	Impaired sensory processing all cerebral levels Lower processing speed/attenuated beta and gamma oscillations-proprioceptive info Recognition and prediction motor actions	Audio-visual	Hearing or visual dysfunction
Vestibular sense	Eye tracking abnormalities Hypo-reactivity and dysfunction Altered vestibular responses and synchrony		Congenital blindness is protective for Sz Visual processing Auditory processing Audio-visual processing

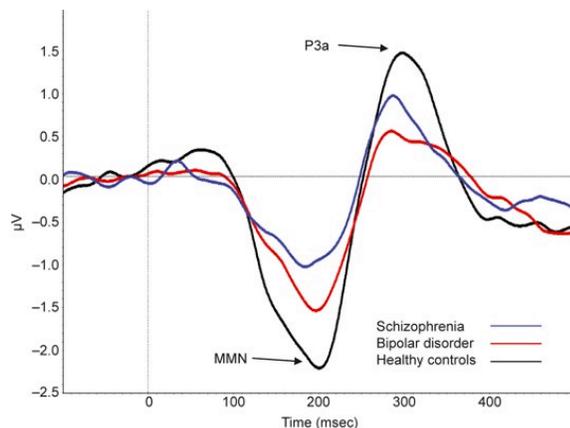
1.1.5. Mismatch negativity and other indexes of auditory processing

These sensory processing abnormalities have been well documented for virtually every sensory domain in all phases of the schizophrenia spectrum, but perhaps best explored in the auditory system, where integrity of sensory function can be assessed using well-characterized evoked related potentials (ERP) such as P50, N100, and, most recently, mismatch negativity (MMN).

Deficits in P50 gating were first described in schizophrenia spectrum disorders in the early 1980s and provided some of the first evidence for deficits in inhibitory processes and subsequently for impaired nicotinic function. Deficits in N100 generation have similarly been documented for over 25 years and have been widely replicated over that time with strong specificity for schizophrenia over other disorders. Both of these potentials are generated within auditory sensory regions and point to breakdown of processing at early stages of stimulus evaluation.

As opposed to P50 and N100, which are elicited in response to simple repetitive stimuli, MMN is elicited pre-attentively when an infrequent deviant sound violates an established pattern of repeated standard sounds[38]. As such, it occupies the interface between sensory/perceptual and cognitive processing. Recent interpretations of the MMN suggest that the temporally-detailed resolution of auditory inputs permits the short-term formation of memory traces of the standard sounds that code predictions of future auditory events. The MMN negative amplitude is thought to signal the prediction error that occurs during implicit perceptual learning when the auditory deviance violates the auditory expectancy[39–42]. Because the echoic memory system, like MMN, functions preattentively, deficits cannot be easily ascribed to impaired attention, emotion, or motivation. To date, MMN constitutes the most sensitive readout of automatic auditory deviance processing, and probably the unique measure for the neurophysiological correlates of echoic sensory memory[39].

Figure 3. Mismatch Negativity in healthy individuals and patients with schizophrenia (from Jahshan, Bipolar Disorders, 2012)



Echoic sensory memory can be modulated by means of pharmacological agents, and these effects can be reliably assessed by changes in MMN. Because MMN depends critically on *N*-methyl-D-aspartate receptor (NMDAR) function[43], the modulation of NMDAR function with pharmacological agents alters the MMN: for example, the NMDA antagonists ketamine and PCP reduce the MMN in healthy subjects[44, 45]. Furthermore, invasive intracortical recording studies in monkeys demonstrated that local infusion of competitive and noncompetitive NMDA antagonists block the generation of the MMN[46]. In addition, neuromodulatory transmitters of NMDAR function, including acetylcholine or serotonin, alter the MMN[47, 48].

Deficits in MMN generation to attributes such as stimulus pitch or duration deviance were first reported in the early 1990s and have been confirmed repeatedly since that time. The reduced MMN amplitude, now well documented in chronic schizophrenia, first episode psychosis, and even individuals at risk for psychosis[21, 36, 49, 50] is thus posited to reflect NMDAR-mediated compromised echoic memory formation and predictive coding[39, 41]. More broadly, many authors have proposed the abnormal regulation of NMDAR by neuromodulatory transmitters as the mechanism that underlies the aberrant functional integration among brain regions in schizophrenia spectrum disorders (i.e., dysconnectivity)[51, 52]. Among the various indexes of early auditory processing, MMN is perhaps the most important ERP, given its role as a potential vulnerability marker for psychosis, and its association with cognitive abilities and psychosocial functioning in normal subjects[31] and in patients with schizophrenia spectrum disorders[55].

Although there is a general convergence of research findings showing reduced MMN amplitude in response to a Frequency-Deviant[56] or a Duration-Deviant[57–61] stimulus, there is also a high degree of variability among studies, with some reporting normal MMN, especially in unmedicated and first episode schizophrenia patients[57, 60, 62–66]. One possible explanation for this heterogeneity is the variable degree of impairment of the fronto-temporal networks underlying processing and temporally-detailed resolution of auditory inputs.

Another hypothesis for inconsistent reports of MMN amplitude reduction is based on the high degree of heterogeneity in the fundamental mechanisms of short term synaptic plasticity found in schizophrenia spectrum disorders[67–74]. Although the neurobiological underpinnings of this heterogeneity are at present unknown, some authors have considered NMDAR hypofunction to be a possible mechanism underlying plasticity deficits[52]. In this context, MMN can be considered an index of experience-dependent short-term synaptic plasticity in the service of auditory sensory/perceptual learning[53], and normal MMN amplitude would indicate intact synaptic plasticity in the prefrontal-temporal neural systems that underlie auditory processing.

From a methodological point a view, a third possible explanation for inconsistent reports of reduced MMN amplitude in patients with schizophrenia spectrum disorders may lie in the different types of deviant stimuli used to elicit MMN, since it appears that that distinct neural populations process different dimensions of auditory deviance[75]. Given the potential for heterogeneity among patients with schizophrenia spectrum disorders in terms of which type of MMN is most affected by their particular variant of the illness, it is convenient to study both Frequency-Deviant and Duration-Deviant MMN, as well as a “Double-Deviant” MMN elicited in response to a single stimulus that combined Frequency and Duration deviance features. Combining deviance features in a single stimulus has previously been shown to enhance the amplitude of MMN in healthy subjects[76, 77], and is theorized to have greater sensitivity to schizophrenia spectrum disorders than stimuli that are deviant in only a single feature[78].

1.1.6. Studying facial emotion processing in schizophrenia spectrum disorders

Above and beyond the auditory system, patients with schizophrenia spectrum disorders demonstrate disrupted spatial and temporal linkage throughout the neural network of facial emotion processing, and these neural abnormalities seem to underlie patients’ emotion recognition and social deficits[79–81]. Impaired facial emotional processing is a cardinal component of schizophrenia-related social deficits[82], and some authors have postulated that it represents an endophenotype[83]. Deficits in facial emotional processing are commonly present early in the course of the disorder, even before the development of frank psychotic symptoms, and typically continue into the chronic phase of the illness even after acute psychotic symptoms resolve after treatment with antipsychotic medication[84]. Indeed, analysis of childhood home movies of patients who later developed schizophrenia spectrum disorders and of their well siblings has revealed subtle abnormalities in facial recognition many years before the onset of overt illness. Deficits in facial emotional processing disrupt the ability to communicate emotions, are associated with worse anxiety, depression, and functional outcomes, and are predictive of poor prognosis[85]. Despite their clinical relevance, currently available psychopharmacological agents are ineffective at remediating impaired facial emotional processing even when they improve psychotic symptoms such as hallucinations.

Facial emotional processing is the result of a well defined process that happens in a neural network that underlies face processing and emotion recognition. Within this neural network, information is processed in a temporally and spatially locked pattern, with basic posterior areas becoming active early, and higher order anterior areas becoming active later. In healthy individuals, this neural network including the occipital face area (OFA), the amygdala, the fusiform gyrus (FG), and the dorsal anterior cingulate cortex (dACC) subserves facial emotional processing [86, 87].

In the seminal study by Haxby et al., face encoding was associated with increased activity in the right medial temporal region including hippocampus and adjacent cortex, with additional cortical activations in an extensive region of left prefrontal cortex (PFC), including left anterior cingulate cortex, midfrontal gyri, inferior frontal gyri and left inferior temporal gyrus. There is also evidence of bilateral or right PFC activation during encoding for nonverbal material. Additionally, face recognition is reported to be associated with increased activity in the medial superior frontal, orbitofrontal, bilateral lateral midfusiform (LMF) and temporal pole regions[87].

The amygdala plays a pivotal role in extracting and processing emotional information from faces[88]. Indeed, emotional faces, especially when presented with low spatial frequency, subliminally, or in unattended peripheral fields, induce robust amygdala activation at latencies between 20-170ms[86],[89]. These activations are thought to facilitate rapid, automatic reactions to salient stimuli and potential threats[88]. Amygdala responses to fearful faces are lateralized with implicit presentations of fearful faces more strongly activating the right amygdala[90] and explicit presentations of fearful faces more strongly activating the left amygdala[91].

The FG is specialized for facial information processing and responds most strongly to faces compared to other complex visual stimuli (e.g., houses)[92]. FG activation peaks roughly 170ms post stimuli presentation and there are strong functional connections between the FG and the amygdala[93]. Early amygdala activity influences FG function during face perception and this influence is shaped by experience, stimulus salience, and emotional content[94],[95].

The existence of a cortical region exhibiting a strong neural response to faces in the lateral occipital cortex (OFA) was demonstrated in early positron emission tomography (PET) and fMRI studies of face and object perception. The OFA has been shown to perform face computations that functionally distinguish it from other face-selective cortical regions. Specifically, the OFA preferentially represents the parts of the face, such as the eyes, nose, and mouth. This representation of face part information is consistent with the OFA acting as the first stage in a distributed network for face perception in which face computations of increasing complexity, such as identity and facial expression discrimination, are performed at higher levels of cortex. The OFA processes face information approximately 100 ms after stimulus onset, an early response consistent with the OFA acting as the first face-selective cortical region. The OFA varies spatially between individuals, with group peak Talairach coordinates placing the OFA in Brodmann area 18 or 19 depending on the study[96].

The dACC is associated with top-down cognitive control of responding to distracting stimuli, including emotional information, during attention-demanding tasks[97]. Indeed, presentation of distracting, irrelevant, fearful faces occupies attentional resources non-volitionally and interferes with task performance[98],[99]. Activity in the dACC modulates amygdala responses to fearful faces at early

latencies, approximately 100ms after stimulus presentation [86], and suppresses responding to irrelevant stimuli allowing for more efficient cognitive responses[99].

Finally, processing emotional faces evokes time-locked neural activity and complex interactions between the amygdala, FG, OFA, and dACC, with these brain regions becoming co-activated or co-deactivated[86],[93],[99].

While the cause of facial emotional processing impairments in patients with schizophrenia spectrum disorders remains unknown, disruptions to the associated neural network may account for some of the deficits. Compared with healthy individuals, individuals at high clinical risk for developing schizophrenia spectrum disorders and patients with schizophrenia spectrum disorders exhibit impaired emotional face recognition[100],[101],[102] and disrupted spatial and temporal linkage throughout the network subserving facial emotional processing[103],[104],[105], with amygdala hyper-activation, FG and dACC hypo-activation[106],[107], and decreased functional connectivity between the amygdala, FG, and dACC[80],[108],[109],[110],[79]. Perhaps most importantly, these neural abnormalities underlie patients' emotion recognition deficits[80, 81, 106, 111].

In neuroimaging studies, amygdala activity evoked by a fearful face was attenuated relative to that evoked by a neutral face in patients with schizophrenia spectrum disorders. However, recent neuroimaging studies suggest that this is due to an increased activation in response to the neutral faces rather than to a decreased response to fearful faces[112]. There is still a quite controversial debate on the activation patterns on the amygdala in schizophrenia spectrum disorders, with studies showing that patients appear to have abnormally increased and sustained amygdala activation when viewing fearful faces relative to low-level baselines, and when viewing neutral faces, as well as at rest. Furthermore, amygdala dysfunction is associated with blunted affect and negative symptomatology suggesting it is functionally linked to social deficits in schizophrenia spectrum disorders.

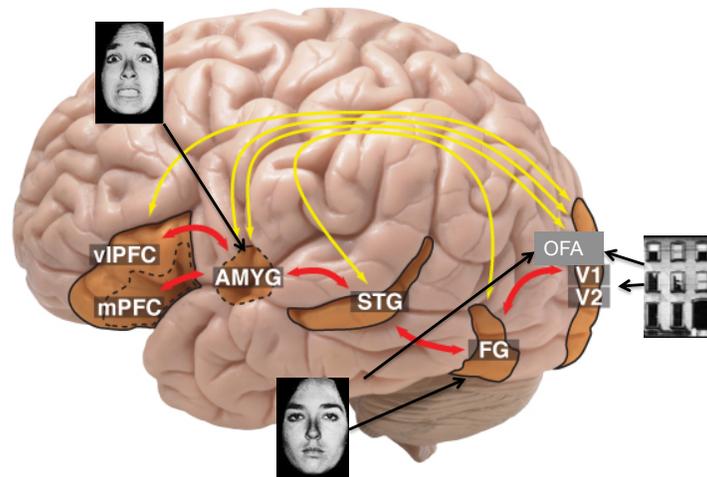
Amygdala-prefrontal circuits, which are critical for affect regulation, have reciprocal relationships with autonomic brainstem arousal circuits, and are disturbed in patients with schizophrenia spectrum disorders. Patients have hypo-activity of vPFC regions with concomitant autonomic hyperarousal during affect recognition tasks, and this pattern is most apparent in patients with poor social functioning. In healthy subjects, labeling negative affect activates the vPFC and proportionally decreases amygdalar activity, likely reflecting a neural network whereby vPFC activity suppresses activation in the amygdala thereby helping to alleviate emotional distress.

Finally, a recent fMRI experiment in schizophrenia spectrum disorders subjects and healthy individuals showed that face selectivity, indexed by the difference in cortical activation between face and tree detection, was significantly reduced in patients for FG, but not for OFA[113]. This finding suggests

boosting visual salience of face images as a potential therapeutic avenue for improving face perception in this psychiatric disorder.

In summary, compared with healthy individuals, patients with schizophrenia spectrum disorders and individuals at high clinical risk for developing schizophrenia spectrum disorders exhibit amygdala hyper-activation, FG, dACC and vPFC hypo-activation, and decreased functional connectivity between the amygdala, FG, and dACC. Together, these data raise the possibility that impaired face processing and heightened amygdalar responses to emotional signals, without effective higher cognitive control neural (e.g., dACC, vPFC) mechanisms for appraisal and cognitive control, could underlie facial emotion processing deficits in patients with schizophrenia spectrum disorders.

Figure 4. A tentative representation of the neural network underlying facial emotion processing



1.2. The behavioral and neurophysiological effects of OT

1.2.1. Oxytocin, bonding and sociality

Oxytocin (OT) is a nine amino acid peptide that is synthesized in the hypothalamic paraventricular parvocellular neurons (PVN) and the supraoptic nuclei (SON) and is then secreted by the posterior pituitary. Projections from the PVN deliver OT to several areas of the central nervous system, including the amygdala, hypothalamus, hippocampus, nucleus accumbens, raphe nuclei, locus coeruleus, vagal centers in the brainstem, sensory neurons, and the sympathetic chain in the spinal cord.

OT has been implicated in bonding, attachment, parenting, and sociality in mammals[114]. In mammals, including humans, affiliative social interactions elicit increases in OT activity, which then activate and integrate 'anti-stress' responses including increased peripheral nervous system activity. This promotes bonding, relaxation and growth, while reducing cardiovascular and neuroendocrine stress responsivity. For example, postnatal OT administration mimics the long-lasting cardiovascular changes caused by stroking in newborn rats and blocks the long-term negative effects of postnatal stress in rats[115] and social isolation in squirrel monkeys[116]. Furthermore, social isolation of the highly social prairie vole decreases respiratory sinus arrhythmia (RSA) and increases depression-like behaviors, and OT administration blocks these effects[116].

The role of OT has been well established in animal research, but over the past decade it has been increasingly shown to be relevant in humans. Early research focused on its core role in parturition, milk ejection, sexual function and parenting. OT is known to mediate autonomic homeostasis integrating afferent input into coordinated sympathetic and peripheral nervous system (PNS) responses. OT has been implicated in multiple autonomic functions including pain, micturition, uterine contractions, lactation, penile erection and multiple aspects of cardiac functioning. Recent studies have focused on its effects on social behavior. In healthy humans, social stimuli such as massage and "warm touch" from a partner increase plasma OT levels and higher OT levels are associated with healthier cardiovascular responses to social stressors. It has also been shown to increase the ability to identify emotions, increase empathy toward others and attenuate aversion to angry faces[117]. Furthermore, plasma OT levels increase after a trust-related but not a non-social task and trust-related OT increases are correlated with autonomic habituation suggesting that individual variation in OT system functioning may determine more general autonomic regulation[118]. Taken together, these findings suggest that the OT system plays a critical role in social behavior.

1.2.2. Dysregulation of the endogenous oxytocin system may contribute to social deficits of schizophrenia spectrum disorders

There is evidence from animal and human models that OT may also play a specific role in the social deficits of schizophrenia spectrum disorders, and disruptions in this system have been implicated in the pathophysiology of schizophrenia spectrum disorders. In healthy subjects, peripheral OT levels increase after entrusting a secret to an experimenter. However, individuals with schizophrenia spectrum disorders do not show this increase and the severity of their negative symptoms predicts their OT response to the situation[119]. Furthermore, cerebrospinal fluid (CSF) OT levels correlate with negative symptoms[120] and plasma OT levels predict schizophrenic patients' ability to identify facial emotions[121]. Additionally, certain OT receptor gene polymorphisms are risk alleles for developing schizophrenia spectrum disorders and are associated with symptom severity[122]. These data support the hypothesis that OT dysfunction may underlie some of the social deficits seen in schizophrenia spectrum disorders.

1.2.3. Oxytocin may be an effective adjunct treatment for social deficits in healthy and clinical populations

Exogenous OT can be safely administered intranasally to humans[123], is well tolerated, and has been shown to have pro-social in healthy and patient populations[124]. In particular, exogenous OT improves in healthy subjects social cognitive abilities and has beneficial neurophysiological effects during social cognition tasks [124],[125]. After intranasal OT administration, healthy subjects rate faces as more trustworthy, have better memory for faces and better emotional face recognition, are better able to infer the mental states of others, have more positive communications, are more generous, gaze more at the information-rich eye region of faces, and demonstrate increased trust behavior when participating in a monetary trust game with human but not computerized opponent[126],[127]. Finally, intranasal administration of OT to healthy subjects inhibits social stress-induced increases in cortisol, increases RSA at rest, and increases PNS activity during affect recognition. Taken together, these data indicate that exogenous OT selectively improves various aspects of social cognition and behavior and raises the possibility that exogenous OT may be an effective adjunct treatment for improving social deficits in multiple patient populations, including autism and schizophrenia spectrum disorders. For example, OT administration to patients with autism improves facial affect recognition, normalizes social behavior in an online ball-tossing game and increases gaze to the eye-region of faces[128].

1.2.4. Behavioral effects of exogenous oxytocin in patients with schizophrenia spectrum disorders

Several small recent preclinical studies have investigated the effects of a single administration of OT on multiple aspects of social cognition in schizophrenia spectrum disorders. The findings are nonetheless mixed. While some studies found that intranasal OT administration improves multiple aspects of social cognition, including affect recognition, theory of mind and trustworthiness ratings[127, 129, 130], others found no significant effects[131, 132].

Additionally, longitudinal clinical trials have been conducted to investigate the long-term effects of OT administration in patients with schizophrenia spectrum disorders. Three recent clinical trials in patients with schizophrenia spectrum disorders found that two, three and eight weeks of intranasal OT administration significantly decreased positive and negative symptoms, although one three-week clinical trial failed to find any effects of intranasal OT on positive symptoms, negative symptoms and social functioning [133],[134],[135]. Clearly, adequately power randomized clinical trials should be conducted to rigorously evaluate the domains in which OT exerts behavioral effects.

Table 1. Intranasal oxytocin treatment trials in patients with schizophrenia spectrum disorders stable on antipsychotic drugs: effects on positive symptoms, negative symptoms, and cognitive deficits (adapted from Feifel et al., 2016, Biological Psychiatry)

Author	Dosing/Duration	Results: Positive Symptoms	Negative Symptoms	Cognitive Deficits
Feifel et al., 2010	40 IU twice daily, 3 weeks/ crossover design	OT improved PANSS positive subscale and CGI after 3 weeks	OT improved negative subscale after 3 weeks	
Pedersen et al., 2011	24 IU twice daily, 2 weeks	OT improved PANSS positive subscale after 2 weeks	OT improved PANSS negative subscale	Improvement in identification of second false beliefs and trends toward significant improvement in accurate recognition of deception and rating untrustworthy faces as untrustworthy (Brune task)
Averbeck et al., 2011	24 IU, single dose	NA	NA	OT treatment improved ability of patients to recognize most emotions (hexagon emotion discrimination test)
Goldman et al., 2011	10 or 20 IU, single dose	NA	NA	10 IU dose decreased emotion recognition due to emotion overidentification. 20 IU dose improved emotion recognition PS vs. NPS, specifically around fear recognition
Feifel et al., 2012	40 IU twice daily, 3 weeks/crossover design	NA	NA	OT improved verbal learning (CVLT) but not working memory (LNS) after 3 weeks
Modabbernia et al., 2013	40 IU twice daily, 8 weeks	OT improved PANSS positive subscale starting at 8 weeks	OT improved PANSS negative subscale after 8 weeks	NA
Lee et al., 2013	20 IU twice daily, 3 weeks	Positive symptoms (BPRS) not improved vs. PL after 3 weeks	Negative symptoms (BPRS) improved in small group of inpatients patients after 3 weeks	NA
Fischer-Shofty et al., 2013	24 IU, single dose	NA	NA	OT improved recognition of kinship (Interpersonal Perception Task)
Davis et al., 2013	40 IU, single dose	NA	NA	OT improved perception of sarcasm, deception, and empathy (EPTT, Eckman

				Facial Recognition Task)
Woolley et al., 2014	40 IU, single dose	NA	NA	OT improved controlled (ability to comprehend indirect expression of emotion, thoughts, and intentions) but not automatic (emotional cues in voices, faces, and body language) social cognition in SCZ
Gibson et al., 2014(38)	24 IU twice daily, 6 weeks	Both OT and PL groups exhibited significant improvement in PANSS positive subscale after 6 weeks	OT improved PANSS negative subscale after 6 weeks	OT but not PL decreased fear recognition and perspective taking component of empathy after 6 weeks (ER-40)
Cacciotti-Saija et al., 2014	24 IU twice daily, 6 weeks	OT did not improve positive symptoms (SAPS) beyond SCT when given in combination with 6 weeks of SCT	Increased use of IN OT, but not PL, was correlated with lower SANS scores	Six weeks of daily OT added to SCT did not enhance the SCT greater than PL
Davis et al., 2014	40 IU twice weekly, 6 weeks	OT did not improve positive symptoms (BPRS) beyond SCT when given in combination with 6 weeks of SCT	Six weeks of OT added to SCT did not improve negative symptoms (CAINS)	Six weeks of OT added to SCT enhanced social cognitive benefits (empathic accuracy) greater than PL, lasting at least 1 month
Michalopoulou et al., 2015	24 IU, single dose	NA	NA	OT improved the "executive component" of working memory (Digispan)
Shin et al., 2015	40 IU, single dose	NA	NA	OT decreased amygdala activity for fearful faces and increased activity (fMRI) for happy faces (Emotion Recognition Test)

BPRS, Brief Psychiatric Rating Scale; CAINS, Clinical Assessment Interview for Negative Symptoms; CGI, Clinical Global Impression; CTL, control subjects; CVLT, California Verbal Learning Test; EPTT, emotional perspective taking task; Exp, experiment; ER-40, The Emotion Recognition 40; F, female; fMRI, functional magnetic resonance imaging; IN, intranasal; LNS, Letter Number Sequence; M, male; NA, not applicable; NPS, nonpolydipsic; OT, oxytocin; PANSS, Positive and Negative Syndrome Scale; PL, placebo; PS, polydipsic; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SCT, social cognitive test; SCZ, schizophrenia spectrum disorders.

1.2.5. The effects of oxytocin on neural system activations in healthy individuals

Recent neuroimaging techniques have allowed scientists to investigate in vivo the neurophysiological correlates of the effect of OT. These studies were mostly conducted using functional Magnetic Resonance Imaging (fMRI) and electroencephalography (EEG). By examining fluctuations in the hemodynamic activity in the brain using fMRI after the administration of OT compared with the administration of a placebo, the network and regions that contribute to OT's influence over brain activity have become clearer. Accumulating evidence suggests that OT plays a key role in the neural circuitry underlying facial emotion processing. OT appears to modulate both regional activity and functional connectivity among a number of brain regions, including the amygdala, the prefrontal cortex (PFC), the fusiform gyrus (FG), and the anterior cingulate (ACC)[136, 137].

In healthy subjects, OT administration decreases amygdalar activation in response to fear-inducing stimuli, reduces coupling of the amygdala to brainstem regions implicated in autonomic and behavioral manifestations of fear stimuli, and increases vPFC activation during an affect recognition task[138]. Furthermore, in one of the few studies to simultaneously measure eye-gaze during an affect recognition task, OT administered to healthy subjects decreased activation of the anterior amygdala in

response to fearful faces but increased posterior amygdala activation possibly due to increased gaze to the eye-region of faces[139]. OT administration also increases FG and dACC activations, and strengthens functional connectivity between the ACC and amygdala during presentation of emotional faces and at rest[140],[137, 141]. Finally, OT polymorphisms are associated with variation in amygdala and brainstem volume in humans[142]. OT appears to influence men and women differently at the level of brain function and behavioral response. There are strong dimorphic differential effects: for instance, OT administration increases amygdala activation in women, but decreases it in men[143].

Studies also examined the reward system after OT administration. OT has an effect over reward-related learning in that it seems to increase activation associated with reward-related learning in the caudate while decreasing learning effects. It has a similar influence on activation in the putamen, but is specific to learning during social interactions. How OT affects neural activity during social tasks in the globus pallidum (GP) is less clear, but it appears to play a role in attachment. Activation in the bilateral caudate was found to be attenuated by OT administration in participants after receiving feedback about the trustworthiness of the partners with whom they had just interacted. In contrast, using a standard prisoner's dilemma paradigm to explore trust, another study found that the left caudate was significantly activated after OT administration in response to trustworthiness in the form of reciprocated cooperation in human opponents, but there was no change in activation in the caudate after unreciprocated cooperation, thus reinforcing the role of the caudate in action contingency. The putamen shows reliable changes in activation only after OT administration during games involving trust manipulations and when there is concurrent activation within the caudate. Therefore, the putamen, along with the caudate, may play a role during the processing of rewards related to interactions with other people[144].

The temporal lobes are also known to be a target of output from the basal ganglia, which may show how OT administration influences neural processes in this area through learning and reward processing of social stimuli. Of the areas in the temporal lobe, the middle (MTG) and superior temporal gyrus (STG) have been shown to be consistently activated in studies involving human facial emotion processing and during mentalizing/theory of mind. Several studies reporting whole brain findings found differential activation in the temporal lobe after OT administration, most of which used faces as social stimuli. In addition, another study found that connectivity to the temporal lobe from the amygdala was increased after OT administration. This consistency of activation made this the most robust region showing activation after OT administration. Of the areas in the temporal lobes associated with social processing, the fusiform gyrus has been the area most consistently activated in response to tasks incorporating facial stimuli and is known to be modulated by facial valence. Neural activity in this area has also been shown to be modulated by OT administration. Variability in task types may explain why OT administration was shown to attenuate activation in the temporal lobes

during implicit facial processing but to increase activation in the temporal lobes during explicit facial processing[144].

Studies using EEG have demonstrated how OT administration can attenuate cortical activity and its association with social tasks. To date, only 5 studies have used EEG and OT in humans and only 2 have explored the social implications of altered cortical activity due to OT administration while performing a task with social stimuli. A few studies have been done using EEG and OT administration without incorporating any social elements. Unsurprisingly, these studies did not find any effect of OT administration. A study by Fehm-Wolfsdorf and colleagues explored the potential for OT administration to facilitate nonsocial learning and long-term recall of 25 unrelated nouns and its effect on auditory evoked potentials using a series of tone pips. Another study by Born and colleagues examined OT administration in participants during an auditory mismatch task; no difference was found in cortical activity after OT administration. Both of these experiments highlight that OT administration did not appear to have any systematic effect on brain activity in tasks lacking social elements[144].

To demonstrate that OT administration can have an effect over cortical activity during social tasks, Perry and colleagues used EEG and OT administration along with stimuli that demonstrated biological motion. Participants were presented with a series of point lights that reflected either biological or nonbiological movements. After receiving OT, participants demonstrated improved performance between trials associated with biological movement and those with random movement, and participants who received OT elicited widespread μ and α suppression compared with those who received placebo. This change in μ/α activity may indicate potential processing of higher social information as well as activation of the mirror neuron system. The study by Perry and colleagues is particularly important, as it highlights the specificity of cortical activity elicited by OT administration in a social context. Their study also highlights the importance of OT administration in manipulating widespread cortical activity and provides a possible translation to the importance of mirror neurons and their association with OT administration. Another study with social stimuli explored the cognitive effects of charitable donations and their modulations by OT administration. Huffmeijer and colleagues measured frontal α asymmetry and parental love withdrawal (i.e., how often parents would withhold love and affection to discipline their children for misbehaving or failing to attend to an instruction) after OT and placebo administration and then gave participants a chance to donate to a charitable organization. They found that in participants with lower degree of love withdrawal and relative lower right to left frontal α activity OT administration increased charitable donations. In addition, participants who showed higher relative left frontal activity gave larger donations than those with higher relative right frontal activity. No differences in frontal α asymmetry were found after OT administration; however, EEGs were recorded only at rest and with no social or cognitive probes, which may be why no changes were observed[144]. Overall, these studies show how using EEG can increase our

understanding of how OT administration exerts its influence over cortical activity in addition to hemodynamic findings and how these changes in neural activity may influence social cognition.

Taken together, these data suggest that intranasal administration of OT may be an effective adjunct treatment for remediating some aspects of impaired information processing and its underlying brain circuitry in people with schizophrenia spectrum disorders. Despite accumulated evidence on the effects of OT on behavioral outcomes in schizophrenia spectrum disorders, the effects of OT on the neural activity underlying auditory processing and facial emotion processing in this disorder have not been investigated widely.

2. SCOPE OF WORK

2.1. Can oxytocin remediate the aberrant neural system activation patterns that characterize schizophrenia spectrum disorders?

In chapter 1, I describe some of the basic sensory and emotion processing abnormalities that characterize the schizophrenia spectrum. Such impairments have been shown to impact social cognitive abilities, and possibly drive deterioration of social functioning very early in the course of illness. Currently, no treatments exist for the social cognitive impairments that affect people with schizophrenia and other neuropsychiatric illnesses, such as autism. More research is clearly needed to identify agents that could target this domain.

In chapter 2, I summarize the effects of oxytocin (OT), a neuropeptide that can be administered safely to humans, has numerous prosocial effects, and has substantial promise as a novel pharmacologic treatment for the social cognitive impairments present in various neuropsychiatric conditions. After a single intranasal dose of OT, healthy subjects show better emotional face recognition, improved memory for faces, and more gazing at the information-rich eye region of faces. Furthermore, a single dose of OT improves facial and prosodic emotion recognition and increases gaze to the eye-region of faces in patients with autism and improves emotional face recognition in patients with alexithymia. Finally, recent work has shown that the intranasal administration of OT to patients with schizophrenia spectrum disorders improves social cognition including emotional face recognition, and reduces negative symptoms.

These data raised the possibility that exogenous OT may be an effective adjunct treatment for improving social cognitive deficits in patients with schizophrenia spectrum disorders; however, the neural mechanisms of these effects remain unknown. fMRI and EEG studies have investigated in vivo the neurophysiological correlates of the effect of OT in healthy populations as well as some clinical populations. Emerging evidence suggests that OT modulates several neural systems in healthy individuals, regulating brain activity in areas like the sensory cortices, the amygdala, the fusiform gyrus and the anterior cingulate. Of course, findings are inconclusive as different paradigms have been used to test the effects of OT, which appear to be context-dependent. Nonetheless, these cortical and subcortical areas are all implicated in information processing, and have shown disturbances in terms of activity and connectivity in various samples of patients with schizophrenia spectrum disorders. This suggests that OT administration may remediate the neural abnormalities underlying sensory processing deficits and facial emotion processing deficits in schizophrenia spectrum disorders.

2.2. Is amygdala modulation the critical mechanism by which oxytocin improves facial emotion processing?

Surprisingly, little is known about the neural effects of OT in patients with schizophrenia spectrum disorders. Only one study to date has investigated the neurophysiological effects induced by OT in patients with schizophrenia spectrum disorders[145]. This was a fMRI study conducted in a small sample of patients with schizophrenia, using a facial emotion processing paradigm. OT decreased amygdala reactivity in response to fearful faces, whereas it increased amygdala activity for happy faces. In addition, OT induced differential effects between the patient and control groups. OT attenuated amygdala activity in patients with schizophrenia, whereas neuropeptide augmented amygdala activity in healthy controls. These results suggested that OT has a differential modulatory effect on amygdala response to emotional faces between patients with schizophrenia and healthy individuals. Given the limited effect of current antipsychotic medications on the impaired ability to process facial emotions for patients with schizophrenia spectrum disorders[146], this was the first study suggesting that OT may be effective in remediating dysfunctional neural activity related to facial emotion processing in those with schizophrenia spectrum disorders. The study only identified effects of OT on the amygdala, while there is ample evidence documenting that the effects of OT occur on distributed neural networks in healthy controls. Nonetheless, this was the first attempt to elucidate the mechanism of action that possibly justifies the OT-induced behavioral effects repeatedly observed in patients with schizophrenia spectrum disorders.

Of course the neural effects of OT in schizophrenia spectrum disorders go beyond the amygdala. For example, a large body of evidence from animal studies suggests that OT administration may normalize amygdala-prefrontal dysfunction in schizophrenia spectrum disorders by targeting first brainstem activity. In rats, OT signaling modulates amygdala projections to hypothalamic and brainstem nuclei that regulate the behavioral and physiological expression of fear and OT signaling within brainstem nuclei strongly regulates autonomic output. It is therefore possible that OT modulates brainstem activity leading to decreased amygdala and increased vPFC activity in patients with schizophrenia spectrum disorders while viewing emotional faces.

Additionally, more knowledge is needed about the effects that OT has on neural oscillatory patterns, as it is becoming increasingly more clear that time sensitive alterations of brain activity are a hallmark of schizophrenia spectrum disorders and shape behavioral responses to the environment. Elucidating the neural mechanisms of how OT administration improves neural activity and behavior is a critical step to developing and optimizing the use of OT as a treatment in schizophrenia and other neuropsychiatric illnesses.

2.3. Studying the effects of oxytocin on brain activation patterns using Magnetoencephalography Imaging (MEG-I)

One neuroimaging technique that permits to address these questions is Magnetoencephalography (MEG). MEG-Imaging is a uniquely powerful tool for investigating neural activation patterns, given its detailed spatial and temporal resolutions. MEG enables a deeper understanding of networks of oscillatory patterns that emerge from specific neural circuits in schizophrenia spectrum disorders, their dysfunction and their response to interventions. There is growing interest in its use in the characterization of neuropsychiatric illnesses.

Compared to other brain imaging methods, MEG-Imaging provides significant advantages. First, MEG typically has many more sensors than EEG allowing for sampling of the scalp magnetic field at very high spatial resolutions (the MEG machine used in this project has for instance 275 channels). Although it has many more sensors than EEG, MEG is often portrayed as a method with limited spatial localization. The accuracy of localization deteriorates with depth, but only slightly unless one is too close to the center of the head. Nevertheless, a recent study has shown accurate reconstructions for deep sources at the level of the amygdala[147].

Second, modern reconstruction algorithms enable estimation of brain activity at very high spatiotemporal resolutions especially for neural oscillations in the range from 2-160Hz, which cannot be directly imaged with other popular functional brain imaging modalities. These features allow detection of important aspects of neural activity such as synchronization and coherence[148] and exploration of neural abnormalities in early and late processing of stimuli in schizophrenia spectrum disorders[149].

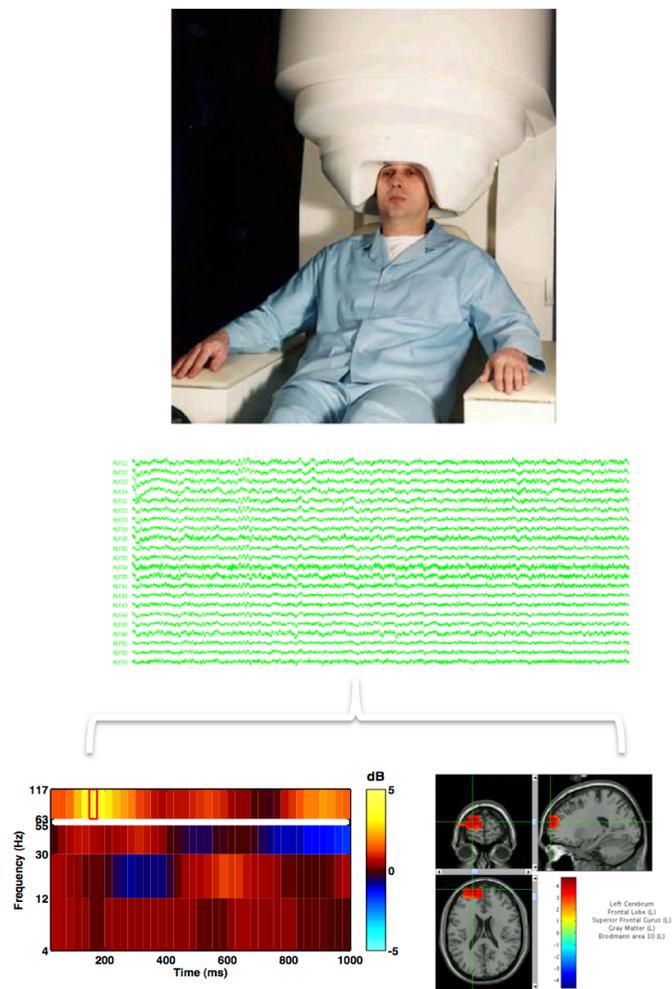
Third, MEG directly measures neural activity and does not rely on cerebral blood flow, which is affected by OT thereby avoiding the potential confounds to which other neuroimaging modalities are sensitive[150].

Finally, compared to EEG, MEG has been shown to be more reliable and have a higher signal-to-noise ratio in studies of schizophrenia spectrum disorders. Because of the millisecond temporal resolution and ability to delineate neural oscillations and localize neural responses within the brain, MEG-Imaging allows for an ideal exploration of neural abnormalities in early and late information processing in schizophrenia spectrum disorders.

To my knowledge, the study hereafter presented was the first study to use MEG-Imaging to study the effects of OT on neural oscillatory patterns in both healthy subjects and patients with schizophrenia spectrum disorders during two well-validated tasks for the assessment of sensory processing in the

auditory and visual domain. The findings from this study will hopefully be of high significance to the field as they: **1)** provide high-impact data on the spatiotemporal features of the neural dysfunction in patients with schizophrenia spectrum disorders, and **2)** Uncover the basic neurophysiological mechanisms at the systems level of OT effects in patients with schizophrenia spectrum disorders and healthy participants. These aspects of OT effects in humans are essentially unknown at the present time.

Figure 1. Data collection and analysis with Magnetoencephalography Imaging (MEG-I).



2.4. Choosing the appropriate experimental paradigms for the study

The overall aim of the study was to use MEG to elucidate the effects of exogenous OT on early sensory processing, as that represents the basic mechanism that is disrupted in schizophrenia spectrum disorders, and leads to a plethora of social cognition deficits, on which OT seems to be effective.

As OT is known to induce differential effects between patients and control group, testing the effects of OT required a double-blind, counterbalanced, placebo-controlled, cross-over, within-subjects design. 40 International Units (IU) of OT or placebo were administered intranasally to patients with schizophrenia spectrum disorders (SZ) and healthy controls (HC).

The choice of the testing paradigms was influenced by the following criteria:

1. early sensory processing should be evaluated both in the auditory and in the visual domains, as OT was shown to behaviorally affect social cognition in these two different sensory modalities;
2. although most effects of OT have been studied in social tasks, and studies using tasks lacking social elements did not report these effects, there is evidence from animal studies that OT may affect non-social information processing. Therefore, paradigms used in the study should allow for an investigation of non-social components;
3. although there are several neuropsychological methods to evaluate early auditory processing, it is desirable to choose a paradigm that consistently demonstrates impairments in schizophrenia spectrum disorders and for which the mechanism of action is adequately conceptualized and demonstrated;
4. although there are several paradigms to evaluate facial emotion processing, it is advisable to choose a paradigm that has been implemented in prior MEG studies and has elicited activity in areas that OT is known to affect in healthy subjects or patients populations;
5. the visual paradigm should concomitantly allow for an exploration of brain activation patterns above and beyond the “usual suspects”, i.e. areas that prior research has already confirmed as affected by OT. It is plausible that identifying areas susceptible to the effects of OT may shed new light of the wide range of activity that OT induces on distributed neural networks.

2.4.1. Experimental paradigm 1: can oxytocin induce changes in mismatch negativity?

As I discussed in Chapter 1, MMN is the most sensitive readout of automatic auditory deviance processing and has been proposed as a vulnerability marker for psychosis, given its consistent

reduction in various schizophrenia spectrum disorders samples and its association with cognitive abilities and psychosocial functioning in normal subjects and schizophrenia patients. There are nonetheless many caveats to this assumption, one being that MMN amplitude is not uniformly reduced across all patients with schizophrenia spectrum disorders, and second that MMN is not a static construct, as demonstrated by NMDA-R based pharmacological experiments. Some authors have in fact postulated that it may serve as an indicator of neurophysiologic changes that occur in the central auditory system. Studies conducted with healthy subjects support this hypothesis, showing persistent MMN improvements after auditory discrimination training. Emerging evidence from studies conducted in schizophrenia spectrum disorders seems instead to cast doubt on this hypothesis. Recently, one study tested the hypothesis that a brief two-week auditory training in schizophrenia patients would result in an increased MMN amplitude, and found significant improvements in verbal working memory[151], but no training-specific effects on MMN amplitude or latency, possibly because of small sample size, narrow range of auditory stimuli, an insufficient number of training sessions to drive neurophysiological changes, and/or lack of reliability of the MMN signal[152]. But, if MMN is a dynamic measure, can OT alter MMN? And if so, what would be the mechanism of action? and what is the relationship between OT and the auditory system?

In order to answer this question, it is critical to incorporate findings from animal studies. OT receptors are distributed in several regions of the forebrain, and this distribution seems to be critical for social behaviors. In fact, a study by Insel and Shapiro in 1992[153] demonstrated that species from the genus *Microtus* (voles) selected for differences in social affiliation showed contrasting patterns of OT receptor expression in brain. By in vitro receptor autoradiography with an iodinated OT analogue, specific binding to brain OT receptors was observed in both the monogamous prairie vole (*Microtus ochrogaster*) and the polygamous montane vole (*Microtus montanus*). In the prairie vole, OT receptor density was highest in the prelimbic cortex, bed nucleus of the stria terminalis, nucleus accumbens, midline nuclei of the thalamus, and the lateral aspects of the amygdala. These brain areas showed little binding in the montane vole, in which OT receptors were localized to the lateral septum, ventromedial nucleus of the hypothalamus, and cortical nucleus of the amygdala. Similar differences in brain OT receptor distribution were observed in two additional species, the monogamous pine vole (*Microtus pinetorum*) and the polygamous meadow vole (*Microtus pennsylvanicus*). Additionally, receptor distributions for two other neurotransmitter systems implicated in the mediation of social behavior, benzodiazepines, and mu opioids did not show comparable species differences. Furthermore, in the montane vole, which shows little affiliative behavior except during the postpartum period, brain OT receptor distribution changed within 24 hr of parturition, concurrent with the onset of maternal behavior. This was the first study that suggested that variable expression of the OT receptor

in brain may be an important mechanism in evolution of species-typical differences in social bonding and affiliative behavior.

Although these findings clearly shed new light on the distribution of OT receptors, but the precise expression pattern of OT receptors and downstream consequences of OT receptor signaling remain unclear. A significant barrier to physiological studies of OT is the lack of adequate OT receptor antibodies suitable for immunohistochemistry and electron microscopy. Previously, receptor distribution was examined by RNA *in situ* hybridization or autoradiography using radioligands, revealing the general anatomical areas believed to express OT receptors. However, autoradiography lacks cellular resolution and synapse-type or cell-type specificities required for in-depth study of neural circuits sensitive to OT. More recently, transgenic methods combined with viral expression systems have been used to tag OT receptors with fluorescent reporters such as GFP or the Venus variant of YFP. These important studies have highlighted several regions and cell types regulated by OT, including somatostatin-positive interneurons of prefrontal cortex involved in sexual behavior, and serotonergic neurons of the raphe nuclei that control anxiety, and project to nucleus accumbens for social reward[154, 155]. One caveat of these approaches is that transgene expression could interfere with the endogenous expression profile, especially given the large number of regulatory elements controlling transcription and tissue-specific localization of the OT receptor.

More recently, OT was shown to affect cortical circuits to enable maternal behavior[156]. In particular, OT enabled mice to recognize the behavioral significance of infant distress vocalizations. Expression of maternal retrieval behavior is enhanced by OT and seems to require plasticity specifically within left auditory cortex to reorganize excitatory and inhibitory inputs for successful processing of pup distress calls[156].

Inspired by these findings, Mitre and colleagues developed specific antibodies for the mouse OT receptor OXTR-2. After purifying and validating these antibodies, they investigated where OT receptors were found in the mouse brain by examining receptor localization across different areas and also in subcellular compartments (including excitatory and inhibitory synapses) using electron microscopy. They identified a distributed network of female mouse brain regions for maternal behaviors that are especially enriched for OT receptors, including the piriform cortex, the left auditory cortex, and CA2 of the hippocampus. Electron microscopic analysis of the cerebral cortex revealed that OT receptors were mainly expressed at synapses, as well as on axons and glial processes. Functionally, OT transiently reduced synaptic inhibition in multiple brain regions and enabled long-term synaptic plasticity in the auditory cortex. The authors concluded that OT modulation is important for regulating excitatory–inhibitory balance and plasticity in the auditory cortex and possibly throughout the brain. More specifically, modulation of inhibition may be a general mechanism by which OT can act throughout the brain to regulate parental behaviors and social cognition.

Taken together, findings from these animal studies suggest that OT induces specific activity in the auditory cortex and possibly enables long-term synaptic plasticity. If so, the MMN reduction that characterizes individuals with SCHIZOPHRENIA SPECTRUM DISORDERS and reflects NMDA-R hypofunction-mediated impairment of synaptic plasticity, could potentially be remediated by the administration of OT. The specific hypotheses tested in this experimental paradigm were therefore the following:

Hypothesis A: Study differences in baseline auditory MMN scores between SZ and HC subjects. On the placebo day, SZ subjects will show reduced MMN amplitude compared to HC.

Hypothesis B: Study whether OT induces changes in MMN in SZ and HC subjects. SZ subjects will show increased MMN amplitude under OT vs PL.

2.4.2. Experimental paradigm 2: can oxytocin induce changes in emotion face processing?

Across various sections of chapter 1 and 2, I described impaired facial emotional processing as a cardinal component of schizophrenia-related social deficits[82], the neural network activated in healthy individuals, alterations of this network in schizophrenia subjects, and finally the effects that OT has on some of these regions in healthy individuals. Earlier in this chapter, I report findings from the one and only fMRI study that evaluated the effects of OT in patients with schizophrenia spectrum disorders.

A quick glance at findings across these studies clearly show that OT effects are not only dependent on gender, but also on the emotional valence of faces, the implicit or explicit nature of facial processing (attended viewing, unattended viewing, emotion discrimination, emotion labeling), and perhaps most importantly, the samples on which the effects were tested. For example, in attended viewing recognition tasks, fear seems to be the emotion that most consistently evokes early responses in the amygdala, and this applies to healthy subjects as well as clinical populations. However the magnitude of fear-induced activity is calculated in contrast with the activity that neutral faces induce, which poses a number of challenges.

A decreased activation observed in the amygdala for example could either mean an increased activation in response to neutral faces, or a decreased response to fearful faces. If we assume that in healthy subjects neutral faces do not evoke amygdala activity, we can assume that the decreased amygdala activation in response to fear-inducing stimuli evoked by OT[140],[141] means that OT attenuates the emotional reaction to fear and makes it similar to that caused by neutral faces, which is an absence of reaction.

In schizophrenia spectrum disorders, there is evidence of an abnormally increased and sustained amygdala activation 1) when viewing fearful faces, compared to low-level baseline 2) when viewing neutral faces, and 3) at rest. The only study that used the same paradigm concurrently in patients with schizophrenia and healthy controls showed that OT attenuated amygdala activity in response to fearful faces in patients with schizophrenia, but augmented amygdala activity in healthy controls. Both these findings contradict prior evidence.

The situation is further complicated if we take into account the differential activities of amygdala subregions. Another study in healthy subjects showed in fact that OT decreased indeed activation of the anterior amygdala in response to fearful faces, but also increased the likelihood of reflexive gaze shifts toward the eye region irrespective of the depicted emotional expression, a patterns that was related to an increase of activity in the posterior amygdala.

Depending on their role in emotion processing and on the spatiotemporal sequence of brain activations during information processing, other regions may or may not be influenced by the effects of the amygdala.

For example, the FG is theoretically a region that processes facial features irrespective of their emotional valence. However, the timing of this processing (around 170 ms post stimulus onset) is usually after an early response from the amygdala (which peaks around 100 ms). This may explain why in HC OT was found to decrease neural responses within the fusiform gyrus when attending to salient facial features, i.e., the eyes of angry faces, which is considered the threat cues that triggers the fear-related arousal[143]. Again, a study that instead looked exclusively at healthy women found that in the contrast between fearful and neutral faces, OT increased the signal in the fusiform gyrus, and this effect was independent of fixation pattern to specific sections of the facial stimuli as revealed by eye tracking.

Finally, another region involved in early processing of face, irrespective of the emotional connotation, is the occipital face area. This area specifically represents sections of the facial stimuli that carry an emotional connotation (eyes, mouth), and is thought to be the face-selective cortical region during facial processing, with peaking activity around 100 ms. Therefore, amygdala activity triggered by fear should not influence its activation patterns. While no studies to date have found effects of OT on early visual processing, oxytocinergic fibers are distributed in primary sensory regions, including the auditory and the visual cortex[157].

The main goal of this study paradigm was to examine the effects of OT administration on neural oscillatory patterns in response to a fear recognition task, using state-of-the-art reconstruction methods. I localized and assessed task-induced neural oscillatory power changes after OT and placebo administration. While I have explored differences under placebo between HC and SZ at a

whole-head level, I decided to limit my specific experimental hypotheses to the three aforementioned brain areas.

Hypothesis A: On the placebo test day, while viewing fearful faces compared to neutral faces, SZ patients will show impaired early activation and disrupted neural oscillations in the amygdala, in the FG, and in the OFA relative to HC. Studying baseline differences between healthy subjects and patients with SZ will provide information on when and where information processing is disrupted in schizophrenia spectrum disorders.

Hypothesis B: When administered OT vs. placebo, SZ patients will show time-locked enhancement of early responses in the amygdala, the FG and the OFA. This will be consistent with increased neural synchronization, as indexed by increased oscillatory patterns across the frequency bands. This hypothesis will clarify if OT administration can remediate some of the neural abnormalities underlying emotional facial processing deficits in schizophrenia spectrum disorders.

3. MATERIAL AND METHODS

3.1. Participants

Over the course of three years, I collected data on 25 male, right-handed patients with schizophrenia-related disorders (schizophrenia, schizoaffective disorder or bipolar disorder with psychotic features), and 25 gender- and age-matched healthy subjects. Patients were less than 5 years from psychosis onset and between 18 and 35 years old in order to minimize potential confounds associated with chronic mental illness and developmental changes in OT at puberty. Patients had to be taking a single atypical antipsychotic for at least six months with no dosage changes in order to minimize medication confounds. Exclusion criteria for patients included currently taking a typical antipsychotic, mood stabilizer, or anticholinergic drug; neurological disorder; and nasal pathology. Exclusion criteria for healthy participants included past or current psychiatric disorders as per DSM-IV criteria and use of psychoactive or cholinergic medications. All subjects must not have had current substance dependence or abuse defined by DSM-IV criteria (except nicotine dependence), must have passed a urine toxicology screen for illicit drugs on each day of testing. Our sample size of 25 per group provided 80% power to detect medium sized effects ($f = 0.26$, $\alpha = 0.05$) using repeated measure analysis of variance (ANOVA).

In the study, only male participants were recruited. This is justified by two reasons. First, OT administration may have sexually dimorphic effects. For example, intranasal OT decreases amygdala responses to fearful faces in men but increases amygdala responses to identical stimuli in women[158]. Second, the relationship between OT responses and sex remains unknown[159]. Given these unknowns, I thought that beginning to investigate the effects of OT only in men would have minimized inter-subject variability and maximized the feasibility of they study. However, I fully acknowledge that women are underrepresented as research participants and that the same research questions apply to a female population. Thus, follow-up studies will include women.

Participants were recruited from the Langley Porter Psychiatric Institute (LPPI) of University of California, San Francisco (UCSF). Based on overall experience recruiting patients with schizophrenia spectrum disorders in this age group, a conservative estimate of dropout (e.g., consenting and enrolling but then not showing up or deciding not to participate) was 10%. I also expected an additional 5% attrition rate for usable data from the two imaging sessions due to subject compliance and artifacts during brain imaging acquisition. Therefore, I recruited 30 patients over the 3-year study or roughly 10 patients per year in order to reach our recruitment goal of 25 patients. Given that the LPPI program alone recruited roughly 25 new patients with recent-onset schizophrenia (of which, two thirds were male) per year over the last three years, I was confident that I would be able to meet our

recruitment goals. Healthy participants were recruited with online and offline advertisements. Participants were paid for travel and their time to help with recruitment and to decrease dropout. All participants received compensation for study participation, and payment was contingent on study participation and not performance. While in the study, patients received treatment by clinicians who were not involved in the study (medication management, psychoeducation, psychotherapy).

3.2. Clinical assessments

I have attended training for the administration of clinical interviews at the UCSF Vinogradov Schizophrenia laboratory located. My assessments have been quality controlled and verified by Dr. Melissa Fisher, director of assessments. I have administered to each participant a standardized diagnostic evaluation using the Structured Clinical Interview for the DSM-IV-TR (SCID) modules for psychotic and mood disorders[160]. I have also administered the Positive and Negative Syndrome Scale to assess symptom severity[161].

3.3. Study protocol

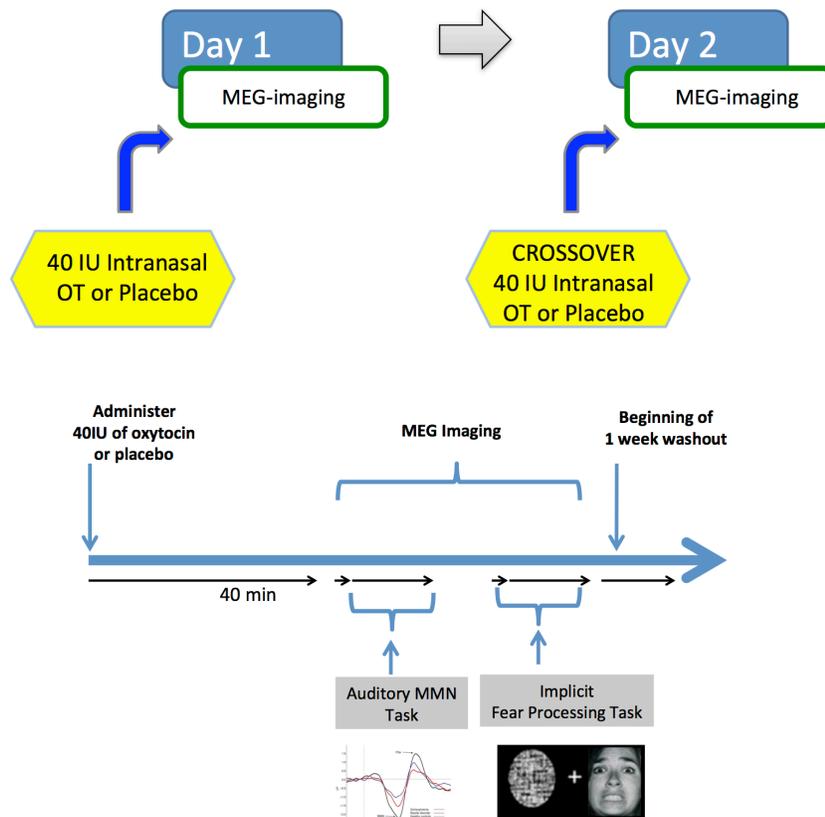
After consenting and clinical assessments, participants were conducted to the UCSF Neuroimaging Center (NIC), a facility that houses a whole body Siemens 3 Tesla MAGNETOM Trio Tim scanner with a 12-channel head coil, neck and spine coils, 16-channel parallel imaging, inline diffusion, perfusion, fMRI BOLD imaging, DTI, and high-resolution anatomical imaging capabilities. This state of the art facility includes hardware and software for presentation of visual and auditory stimuli as well as the recording of button press, eye-movement, galvanic skin response, pulse oximetry, respirations, and EKG. A staff physicist oversaw all imaging research; a Siemens physicist was present at the site full time, and a staff research associate is available to assist with scanner operation. Structural MRI from all participants were collected and stored in secure UCSF servers.

Next, participants were conducted to the The Biomagnetic Imaging Laboratory (BIL), a 1200 square foot space located in the Department of Radiology at UCSF. The BIL currently houses a whole head 275 channel MEG system (Omega 275, CTF Inc. Port Coquitlam, BC Canada). This system has 275 axial gradiometer MEG sensors distributed over the whole cortex, with 29 reference channels used for noise cancellation, EOG/EMG, ADC/DAC, triggers and 128 channels of simultaneous EEG. All channels may be used simultaneously and are managed by a common hardware interface, signal-processing unit and acquisition workstation computer. The system comes with CTF's advanced processing and analysis software (SAM). The MEG system has a sensor density (2.2 cm), with whole head coverage. The OMEGA 275 has FDA 510K clearance for scanning of the brain.

Prior to undergoing the MEG sessions within a magnetically-shielded room, participants were tested using a urine toxicology screen. Next, 40 IU intranasal OT or placebo were administered intranasally to each participant. MEG recording started 40 minutes after drug administration and continued for no longer than 2 hours. Previous studies have shown that OT has robust behavioral and neural effects at this dosage with this delay[162, 163].

In each session, participants underwent two well-characterized paradigm: a multideviant MMN paradigm and an implicit fear processing paradigm. This was a double-blind, cross-over, within-subject design. After completing the first session, participants waited a minimum of a 1 week washout period. They were then scheduled for a second MEG in session in which the other substance under evaluation was administered, prior to beginning the MEG recording part of the experiment. The Committee on Human Research at University of California San Francisco, approved all study procedures.

Figure 1. Diagrams of study design and experimental protocol.



3.4. Multi-deviant mismatch negativity paradigm

3.4.1. Mismatch negativity paradigm

I assessed three types of MMN using a two-Deviant paradigm and a single-Deviant paradigm. The two-Deviant paradigm assessed Frequency-Deviant MMN and Duration-Deviant MMN (FREQ_DUR). In this paradigm, 80% of the stimuli were standard tones (50 msec, 633 Hz), 10% were Duration Deviants (DUR: 100 msec, 633 Hz), and 10% were Frequency Deviants (FREQ: 50 msec, 1000 Hz). The single-Deviant paradigm assessed the MMN elicited by a Frequency + Duration “Double-Deviant (DBL) stimulus. In this paradigm, 90% of the stimuli were standard tones (50 msec, 633 Hz), and 10% were Double-Deviants (DBL: 100 msec, 1000 Hz). Across paradigms, all tones had 5 millisecond rise/fall times and were presented with a 500 millisecond stimulus onset asynchrony at 78 dB sound pressure level via Etymotic ER3-A insert earphones. The paradigms were administered in four separate blocks (two blocks of the two-Deviant paradigm, two blocks of the Double-Deviant paradigm) lasting approximately 5 min each, with each block comprising a fixed pseudorandom sequence of 300 tones. The order of the four MMN blocks (DBL x2, FREQ_DUR x2) was randomized. In order to reduce the influence of attention on the MMN measurements, subjects were instructed to ignore auditory stimuli while watching a neutral presented on a video display (for MMN task details, see Perez et al., 2012)[50].

3.4.2. EEG data acquisition and preprocessing

EEG activity during the MMN paradigms was recorded in the SZ and HC participants. EEG data were acquired using 128 channels of simultaneous EEG. Continuous EEG data were digitized at a rate of 1024 Hz, referenced offline to averaged earlobe electrodes, high-pass filtered at 1 Hz, and segmented into 1000 ms epochs time-locked to the onsets of the various types of auditory stimuli (-500 to 500 ms). Vertical and horizontal electro-oculograms, recorded from electrodes above and below the left eye and at the outer canthi of both eyes, respectively, were used to correct EEG for eye movement and blink artifacts using a regression-based algorithm[164]. Following baseline correction (-50 to 0 ms) of each EEG epoch, electrodes containing epochs with outlier values were replaced by interpolated values based on a routine implemented in a previously published automated EEG data cleaning algorithm. Specifically, a spherical spline interpolation was applied to any channel and epoch determined to be a statistical outlier ($|z| > 3$) on one or more of four parameters, including variance (to detect additive noise), median gradient (to detect high-frequency activity), amplitude range (to detect pop-offs), and deviation of the mean amplitude from the common average (to detect electrical drift). Subsequently, epochs were rejected if they contained amplitudes greater than ± 75 mV in any of the

electrodes included in the analysis: F3, Fz, F4, C3, Cz, C4.

In the next step, ERP averages for all stimulus types were determined using a sorted averaging method shown to reduce noise in the MMN waveform by averaging over the subset of trials that optimizes the estimated signal to noise ratio (eSNR) for each subject [75]. The number of trials contributing to ERP averages did not differ between groups (all p s > .14). Following sorted averaging, ERPs for all stimulus types were low-pass filtered at 30 Hz, and then standard tone ERP waves were subtracted from deviant tone ERP waves to derive difference waves. The MMNs were then identified in individual difference waves as the most negative peak between 160 and 290 ms for duration-deviant stimuli, and between 90 and 290 ms for the remaining deviant types. The selection of a later, 160 ms starting latency for the duration-deviant MMN search window was to avoid selecting the first peak in the grand average, which was too early in its latency to represent the long duration-deviant MMN. MMN amplitudes were quantified as the mean microvolt value within a ± 10 ms time window surrounding each MMN peak.

3.4.3. Statistical correction for normal aging effects

Given the broad age range of our SZ sample (minimum was 18, maximum was 36), additional steps were taken to control for normal brain development and aging effects. To this purpose, we used EEG data from 121 healthy normative subjects who had previously completed the same MMN paradigm. Normal aging effects on the MMN were modeled in the healthy normative subjects (age range 12–43 years) by regressing the MMN amplitudes on age separately for each Deviant type and electrode. Next, resulting regression models were used to derive predicted normal MMN amplitudes for each study participant (SZ and HC) based on their specific age. Finally, we divided the differences between observed and age-specific predicted MMN amplitudes by the standard error of regression (from the HC regression model), yielding age-corrected MMN z-scores. These z-scores represent, in standard units, the degree to which a participant's (SZ or HC) MMN amplitude deviates from the normal value expected for their age. Accordingly, more positive z-scores indicate smaller MMN amplitude relative to healthy normative subjects (i.e., a greater MMN deficit).

3.4.4. Planned analyses

First, group differences between HC and SZ in MMN age-corrected z-scores under the effects of placebo were assessed using a 4-way repeated measures Analysis of Variance (ANOVA). The ANOVA had Group (SZ, HC) as the between-subjects factor and Deviant Type (DUR, FREQ, DBL), Fronto-Central Lead (Frontal, Central), and Lateral Lead (Left, Midline, Right) as within-subjects

factors. Significant effects were parsed using follow-up F-tests tests of simple main effects. Greenhouse-Geisser non-sphericity correction was applied to within-subjects effects with more than two levels.

Given the absence of lateral lead effects in the baseline ANOVA and the finding of a MMN deficit on frontal sensors, frontal MMN z-scores were averaged over the (F3, Fz, F4) and used as the metrics for subsequent analyses. Change in MMN z-scores as a function of OT/placebo in SZ and HC was assessed using 3-way repeated measures ANOVA on frontal MMN Z scores with 1 between-subjects factor [Group (SZ, HC)] and 2 within-subject factors [Drug (OT, PL), Deviant type (Freq, Duration, Double)]. Significant effects were parsed using *post-hoc* Tukey-Kramer tests. Greenhouse-Geisser non-sphericity correction was applied to within-subjects effects with more than two levels. Alpha was set to $p = 0.05$, two-tailed, for all statistical tests.

3.5. Implicit fear processing task and paradigm

Emotional face processing engages neural generators oscillating at different frequencies distributed in time and space[165]. A multidimensional evaluation of oscillatory power changes detected by MEG-I along frequency, time, and spatial dimensions allows definition of latencies of significant regional brain activation and the stage of cortical and subcortical processing elicited during emotional face processing. As the adaptive modulation of early sensory information processing has been shown to be impaired in schizophrenia spectrum disorders and appears to govern concurrent attentional task performance, I looked at early activations[166].

Some authors have hypothesized that lower activity in schizophrenia spectrum disorders in key regions during emotional processing is not due to an overall average single trial reduction, but to particularly reduced isolated responses in individuals with schizophrenia spectrum disorders. Intra-individual variability could indeed account for differences in neural changes across groups. By examining variability across single trials within an individual, time frequency analysis permitted to test the hypothesis related to increased intra-individual variability in schizophrenia spectrum disorders. Additionally, the use of a within-subject design permitted to detect OT-induced changes even if there is more intra-individual variability in patients than in controls and to investigate whether OT decreases this variability. Using state-of-the-art reconstruction methods, I localized and assessed task-induced neural oscillatory power changes after OT and placebo administration during an implicit fear processing task.

3.5.1. Behavioral task

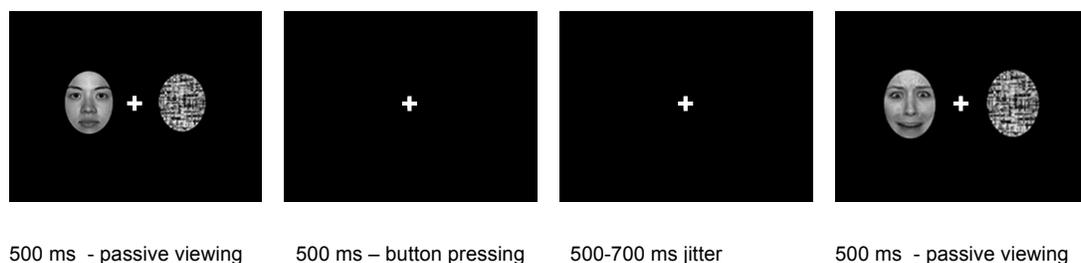
Due to hemispheric specialization in fear processing, I chose a well-validated task indexing implicit processing of fearful expressions in order to maximize the ability to assess lateralized neural responses in the right hemisphere. The task was adapted from Hung et al.[86], and has been shown to elicit MEG-I detectable activations in the amygdala, dACC, and FG[86], [167]. The task was chosen to assess fear processing under conditions requiring attention and response selection with minimal demands on verbal encoding, working memory, and executive function.

In each trial, a task-irrelevant face expressing either fear or a neutral expression was located randomly in either the left or right hemifield, separated by a central fixation cross from a brightness- and contrast-matched scrambled pattern in the other hemifield. Participants fixated on the central cross. See Figure 2. Stimuli were presented for 500ms. After the cross disappeared, participants were instructed to respond to the scrambled pattern by pressing buttons corresponding to the target location. The time window for button pressing was presented for 500 ms, and it was followed by a 500-700 ms jittered period. The task included 200 trials, including 100 trials with the face in each hemifield (50 trials of each expression: neutral and fearful). In order to prevent habituation to the stimuli, different face stimuli were used for each task on each testing day. For task 1, 200 unique faces were selected from three facial expression databases: the Pictures of Facial Affect of Ekman and Friesen[168], the Cohn–Kanade database[169] and the JACFEE database[170]. All databases are well validated in terms of expression identity, intensity, clarity, genuineness, and valence. Images were normalized to the same overall intensity and contrast. Tasks were designed using e-Prime 2.1 (Psychology Software Tools, Inc.). Task behavioral stimuli were synchronized with MEG triggers and successfully incorporated task markers into the MEG-I recordings. All stimuli were back-projected onto a screen positioned approximately 75cm from the participant. A fiber-optic button box was used to record behavioral responses using the dominant hand.

3.5.2.Planned analyses for behavioral responses

The use of a within subject design increased the ability to detect OT-induced behavioral changes separately for patients and healthy participants. Independent samples t-test were used to examine differences during the placebo day. Paired-samples t-test were used in HC and SZ separately to examine whether OT alters accuracy and reaction time in detecting emotional and neutral faces presented in both hemifield. Finally, I used repeated measure ANOVA with drug as a within subject factor and diagnostic group as a between subject factor, to explore second-order effects, comparing OT-induced changes between patients and healthy participants.

Figure 2. Implicit fear processing task.



3.5.3. Image acquisition and pre-processing

Neuromagnetic data were collected with a 275-channel whole-head MAGNETOM Trio Tim scanner. Twenty-nine reference sensors were used to correct distant magnetic field disturbances by calculating a synthetic third order gradiometer. Head location was measured at the start and end of each task run using three magnetic coils attached to the fiducial landmarks, with inclusion contingent on <6mm translations in head movement.[171] MEG-I data were sampled at 1200 Hz and acquired under a bandpass filter of 0.001-300Hz. Data were de-identified, encrypted, and stored in the USCF BIL directories.

MEG epochs consisted of data -500 to 500 msec relative to the onset of the face/scramble stimulus. Epochs were excluded if they contained artifacts or participant responses outside a window of 0.5s to 1.5s post-trial onset. For neural analyses, only data from successful trials was analyzed to control for differences in performance between participants. Artifacts were defined as magnetic flux exceeding 2.5pT tested at 9 frontal sensors, under a temporary bandpass filter of 1-50Hz. If more than 20 epochs included artifact, problematic sensors were removed and data reexamined. An individual's data were excluded if more than 5 sensors were removed, or less than 50 trials remained in either session. On epochs remaining after these rejections, unfiltered sensor data were submitted to source localization to obtain cortical and subcortical activity. The aforementioned actions were operationalized through a preprocessing shell that I developed using Python 2.1. Separate session files were created for neutral and fearful trials.

Anatomical T1-weighted MRI images were collected for each research subject utilizing 3D magnetization prepared rapid gradient echo MRI (160 1-mm slices; field of view = 260mm, matrix = 256×256, echo time = 6 msec, repetition time = 35 msec, flip angle = 30°). A multiple spheres head model was calculated for each sensor relative to the volume using the softwares MRIVIEWER and DipoleFit. Anatomical T1-weighted MRI images were co-registered with MEG data via fiducial

landmarks and the multiple spheres head model. MRI images were spatially normalized to the standard Montreal Neurological Institute template brain using SPM8. White and grey matter segmentation was performed on the Montreal Neurological Institute brain, providing the white/grey matter interface, which served as the solution space for the estimated current generators.

3.5.4.Exploratory time-frequency analysis

The exploratory time-frequency analysis was initially used to spatiotemporally estimate neural sources and examine differences between SZ and HC under the effects of placebo. Time frequency analysis allows for examination of variability across single trials within an individual[172] and provides an overall measure for each individual at each voxel x time that includes inter-individual variability when submitted to group analyses.

Preprocessed data were used to whole-head reconstruct induced oscillatory activity during the 500 ms period following stimulus onset by using the Neurodynamic Utility Toolbox for MEG (NUTMEG[172]). NUTMEG uses a variety of machine learning algorithms to compute source localization of activity on a single trial basis for each voxel x time window, for active (fearful face) relative to control contrasts (neutral face)¹. NUTMEG has a 5mm voxel resolution and computes oscillatory power in the theta (4-7Hz), alpha (8-12Hz), beta (12-30Hz), gamma (30-55Hz), high gamma (65-90Hz) and ultra-high gamma (90-115Hz) range. Computations were performed on the shared computing cluster at the California Institute for Quantitative Biomedical Research (www.qb3.org). These utilized frequency-optimized windows (theta/alpha: 300 msec, beta: 200 msec, low gamma: 150 msec, high gamma: 100 msec), sliding every 25 msec, to calculate noise-corrected pseudo-F ratios relative to a fixed pre-stimulus window of the same duration. To avoid mislocalizations from temporally-correlated sources, each hemisphere was analyzed separately. When the resulting neural activity for each subject for each session was spatially normalized using SPM8, this generated a series of voxels of potential source-locations.

The Statistical nonParametric Mapping toolbox (SnPM)[173] is implemented within NUTMEG to ascertain significant differences across the cortical surface, and includes a variety of standard statistical correction options to account for multiple comparisons. Thanks to SnPM, three-dimensional average and variance maps across subjects were calculated at each time-frequency point and smoothed with a 20x20x20mm³ Gaussian kernel. From this image, a pseudo-t statistic was obtained at each voxel and time window for each frequency band, with t distributions created from 10,000 permutations of the voxel labels. Between-drug (OT vs PL) analyses within a group were conducted using paired tests, while between-group (SZ vs HC) analyses utilized unpaired tests. To reduce false positive results (spurious activation), a spatial threshold of 20 contiguous 5mm voxels showing activity

at 2-tailed t-values corresponding to $p < .05$ was applied prior to querying t-maps for foci of peak activity. Foci t-values were then translated to p-values to determine and report the actual levels of significance. Reported onset and offset latencies were derived at $P < .005$.

3.5.5. Time-locked responses in regions of interest

The exploratory time-frequency analysis confirmed the presence of differential early activations in the fearful/neutral contrast in SZ subjects relative to HC in some regions of interest, specifically the occipital face area and the amygdala, under the effects of placebo. MNI coordinates corresponding to the centroid of these areas were identified in each individual. Broadband activity at each time point in fearful trials was then extracted from these a-priori locations using the adaptive spatial filtering functions available as part of the CTF MEG™ software package (Synthetic Aperture Magnetometry, SAM CTF, version 5.0; VSM Medtech, Inc., Port Coquitlam, Canada; www.ctfmeg.com). Through SAM CTF, MNI coordinates were entered to identify MEG space voxel coordinates with peaks of activation. Localized trial-by-trial time series of the induced oscillatory activity were then averaged across fearful trials for each subject. This 3D matrix (lead field component x sensors x voxel) was then root-mean-square transformed. By taking the square root of the sum of the squares of the three components, I collapsed over the lead field components to get a 2D matrix of sensors x voxels. The average oscillatory activity was finally z-normalized using the -500 ms priori to stimulus onset for comparisons across drugs and group. This procedure was conducted for each hemisphere separately.

Next, in each ROI, an analysis of the maximum z-amplitude from 0 to 250 msec was conducted across hemisphere and group to examine which time window captured the optimal early peak activation (M100). The latency identified across-hemisphere from each individual time series and the latency identified in the across-group x hemisphere grandaverage time series indicated the maximal latency obtained in the broadband response occurred consistently between 50ms and 150 ms post stimulus-onset in the occipital face area and between 150ms and 200 ms post stimulus onset in the right amygdala. Average amplitudes from these time windows were consequently used to assess and compare M100 responses during the presentation of fearful faces. For the purposes of this dissertation, I have finished to analyze data source-localized to the bilateral occipital face area (OFA) and to the right amygdala. The time-frequency analysis indicated additional regions that will continue to be analyzed in future studies.

3.5.6. Planned contrasts for neural responses

To identify implicit fear-related activations, NUTMEG computes the difference in task-induced oscillatory power between fearful and neutral face trials for each latency component for each subject. SnPM unpaired t-tests were used on foci of peak activity to conduct between-group analyses in the placebo day. This indicated which areas showed significant differences in terms of spatiotemporal patterns of early activation (0-500 ms post-stimulus onset) in SZ and HC.

Second, I used SnPM paired t-tests separately for patients and healthy participants to examine how OT affects neural oscillatory power. This analysis indicated which areas - at a group level - show significant differences in terms of spatiotemporal patterns of early activation because of OT.

For the time-locked analyses, average amplitudes from post-stimulus-onset time windows were used as a proxy of the M100 response during the presentation of fearful faces. I used repeated-measures ANOVA to test hypothesis in the a priori regions with factors of Hemisphere (Left, Right), Drug (Oxytocin, Placebo), and Diagnosis (Healthy, Patient). Finally, tests of significant interactions obtained within full-factor ANOVA further characterized effects. Results from these analyses would indicate whether OT affected M100 differentially in HC and SZ in regions where SZ showed impaired early activation patterns relative to HC.

4.1. RESULTS

Demographics and clinical characteristics for enrolled schizophrenia spectrum disorders (SZ) subjects are presented in Table 1.

Table 1. Demographics for schizophrenia spectrum disorders subjects (n=25).

Variable	Mean/N SD/%	
Age	28.1	6.4
Education Level (y)	13.2	1.5
Duration of illness (y)	7.0	4.4
Numbers of previous hospitalizations	4.6	4.0
PANSS Total Score	59.2	15.6
Diagnosis		
Schizophrenia	15	60
Schizoaffective	7	28
Bipolar Disorder with Psychosis	3	12
Access to mental health services		
Seeing a psychiatrist	11	44
Seeing a case manager/nurse practitioner	7	28
Seeing a psychotherapist	7	28
Medications		
Unmedicated	2	8
Taking antipsychotics	23	92
Antipsychotic medication	Mean dose (mg)	Range (mg)
<i>Olanzapine (N = 5)</i>	15	4–30
<i>Risperidone (N = 4)</i>	3	1–8
<i>Quetiapine (N = 6)</i>	344	200–600
<i>Clozapine (N = 1)</i>	328	-
<i>Ziprasidone (N = 1)</i>	89	-
<i>Aripiprazole (N = 2)</i>	12.5	10–15
<i>Paliperidone (N=2)</i>	9	-

The 25 enrolled healthy controls (HC) were gender- and age-matched. None of them had past or current diagnosis of psychotic disorders as per DSM-IVTR criteria, used psychoactive or cholinergic medications, had current substance dependence or abuse defined by DSM-IV criteria (except nicotine dependence). All of them passed a urine toxicology screen for illicit drugs on each day of testing.

There were no differences between the two groups in age, handedness, and years of education. Please see table 2 for means, standard deviations, and statistics. Handedness was analyzed with

Pearson chi-square tests. The remaining demographic variables were analyzed with independent samples t-tests.

Table 2. Baseline differences between schizophrenia spectrum disorders patients and healthy controls.

	Schizophrenia spectrum disorders Patients (n = 25)		Healthy Controls (n = 25)		t	df	p-value
	Mean	SD	Mean	SD			
Age, years	23.75	4.16	21.98	3.60	1.71	49.00	0.09
Education, years	13.00	1.78	12.72	2.95	0.41	49.00	0.69
Handedness						0.248	0.884
Right	23	0.92	26	0.88			
Left	1	0.04	2	0.08			
Ambidextruous	1	0.04	1	0.04			
DBL MMN z-score	0.35	0.99	0.11	0.71	1.82	49.00	0.002
DUR MMN z-score	0.34	0.92	0.04	0.86	1.93	49.00	0.001
FREQ MMN z-score	0.32	1.00	0.09	0.73	1.77	49.00	0.001

FREQ = Frequency Deviant, DUR = Duration Deviant, DBL = Frequency + Duration Double-Deviant

4.1. Experimental Paradigm 1: mismatch negativity

4.1.1. Group differences between healthy controls and schizophrenia spectrum disorders patients in mismatch negativity under placebo

In the HC group, baseline DUR and FREQ MMN Z scores were moderately correlated ($r = .52$, $p = .000$). DBL MMN similarly correlated with FREQ MMN ($r = .65$, $p = .000$) and DUR MMN ($r = .50$, $p = .000$). In the SZ group, baseline DUR and FREQ MMN Z scores were moderately correlated ($r = .43$, $p = .000$). DBL MMN similarly correlated with FREQ MMN ($r = .57$, $p = .000$) and DUR MMN ($r = .54$, $p = .000$). This suggests similar contributions of Frequency deviance and Duration deviance to the Double-Deviant MMN in both groups.

I present here results from the 2x3x2x2 ANOVA on data collected from the placebo day, with Group (HC vs SZ) as a between-subject factor, and Deviant Type, Lateral Lead and Frontocentral Lead as within-subject factors. There was a significant group effect, with MMN amplitude reduced in the SZ group relative to the HC group. In the ANOVA of MMN Z scores, a significant ($p = 0.004$) Group x Fronto-Central Lead x Deviant Type interaction emerged (see Table 1). This three-way interaction was parsed several ways. First, the Group x Fronto-Central Lead effect was examined for each Deviant

Type and found to be significant for the DBL MMN ($p=.006$), but not for the DUR or FREQ Deviant MMN. Further parsing of this Group x Fronto-Central Lead interaction for DBL MMN indicated a significant Group effect at Frontal leads ($p=.003$), with SZ showing MMN deficits ($M= .51$, $SD= .96$) compared to HC ($M = .02$, $SD = .99$), but not Central leads ($p=.102$). Second, the Fronto-Central Lead x Deviant Type interaction effect was examined separately by Group. This two-way interaction was only significant in the SZ group ($p<.001$), with follow-up tests showing a significant Fronto-Central Lead effect for DBL MMN (with greater MMN deficit at Frontal relative to Central leads), but not for DUR or FREQ MMNs. Third, the Group x Deviant Type interaction effect was examined separately at Frontal and Central leads, but in neither case was this effect significant. Taken together, these analyses suggest the presence of a DBL MMN amplitude deficit over frontal leads in the SZ group compared to the HC group. Please see Table 3 for results of the ANOVA of MMN amplitude.

Table 3. ANOVA of MMN Z score differences under placebo.

Effect	DF	F	p value	Follow-up tests*
Group	1,49	6.225	0.014	SZ > HC
Deviant Type (DUR, FREQ, DBL)	1.929	0.493	0.604	
Fronto-Central Lead (Frontal, Central)	1	1.576	0.211	
Lateral Lead (Left, Midline, Right)	1.763	2.976	0.059	
Group*Deviant Type	1.929	0.386	0.672	
Group*Fronto-Central Lead	1	0.944	0.333	
Group*Lateral Lead	1.763	2.098	0.131	
Group*Lateral Lead*Deviant Type	3.374	0.565	0.659	
Group*Fronto-Central Lead*Deviant Type	1.989	5.58	0.004	
Group*Fronto-Central Lead for DUR	1	0.429	0.513	
Group*Fronto-Central Lead for FREQ	1	0.064	0.801	
Group*Fronto-Central Lead for DBL	1	7.715	0.006	
Fronto-Central Lead effect in HC	24	0.243	0.808	
Fronto-Central Lead effect in SZ	24	4.336	0.000	Frontal > Central
Group Effect at Frontal Leads	1,49	9.088	0.003	SZ > HC
Group Effect at Central Leads	1,49	2.706	0.102	
Fronto-Central Lead *Deviant Type in HC	1.994	0.018	0.982	
Fronto-Central Lead *Deviant Type in SZ	1.832	10.659	0.000	
Deviant Type effect at Frontal Leads	1.964	2.571	0.082	DBL > DUR
Deviant Type effect at Central Leads	1.975	0.393	0.673	
Fronto-Central Lead effect for DUR	49	-0.906	0.369	
Fronto-Central Lead effect for FREQ	49	-0.169	0.866	
Fronto-Central Lead effect for DBL	49	4.336	0.000	Frontal > Central
Group*Deviant Type at Frontal Leads	1.917	1.43	0.241	
Group*Deviant Type at Central Leads	1.939	0.234	0.785	

Group*Fronto-Central Lead*Lateral Lead	1.77	0.702	0.480	
HC = healthy controls, SZ = schizophrenia spectrum disorders participants FREQ = Frequency Deviant, DUR = Duration Deviant, DBL = Frequency + Duration Double-Deviant *Between group comparisons are based on independent t-tests. Between lead comparisons are based on Helmert contrasts.				

4.1.2. Effects of oxytocin and placebo on mismatch negativity in schizophrenia spectrum disorders subjects and healthy controls

Armed with information from the baseline ANOVA, I collapsed across lateral leads and selected only frontal MMN Z scores. I then conducted a 3-way repeated measures ANOVA with 1 between-subjects factor [Group (SZ, HC)] and 2 within-subject factors [Drug (OT, PL), Deviant type (Freq, Duration, Double)]. I found a marginally significant *Drug x Group x Deviant Type* ($F=4.976$, $p=.007$). The 3-way interaction was parsed in two ways. First, the *Drug x Group* effect was examined for each Deviant Type separately, and found to be significant for DBL MMN ($p=.032$), but not for DUR ($p=.349$) or FREQ ($p=.441$) MMNs. For DBL MMN, the SZ group showed a significant improvement in MMN amplitude under the effects of OT ($p= 0.003$), whereas the HC group showed no significant drug-induced changes (see Table 4 and Figures 1 and 2). Second, the *Drug x Group x Deviant Type* effect was examined for each group separately. Here I found no significant *Drug x Deviant Type* interactions for HC or SZ. Taken together, these findings suggest that in SZ, OT improves the amplitude of the MMN evoked potential. No significant changes were observed between OT versus placebo in HC.

Table 4. ANOVA of Drug Effects on Mismatch Negativity (MMN) for Schizophrenia spectrum disorders Subjects and Healthy Individuals.

Effect	DF	F	p value	Follow-up tests
Drug	1	0.01	0.919	
Group (SZ, HC)	1	2.004	0.163	
Deviant Type (DUR, FREQ, DBL)	1.942	0.789	0.454	
Drug * Group * Deviant Type	1.977	4.976	0.07	
Drug * Group for DUR	1	0.894	0.349	
Drug * Group for FREQ	1	0.603	0.441	
Drug * Group for DBL	1	4.831	0.032	
Drug Effect in SZ	1,24	9.088	0.003	OT> PL
Drug Effect in HC	1,24	2.706	0.202	
Group Effect in PL	1,49	9.088	0.003	SZ > HC
Group Effect in OT	1,49	0.894	0.349	
Drug * Deviant Type for SZ	1	0.143	0.707	
Drug * Deviant Type for HC	1	1.343	0.252	

HC = healthy controls, SZ = schizophrenia spectrum disorders participants, OT= oxytocin, PL = placebo
FREQ = Frequency Deviant, DUR = Duration Deviant, DBL = Frequency + Duration Double-Deviant

Figure 1. Effects of oxytocin on Double-Deviant (DBL) MMM Z scores in schizophrenia spectrum disorders subjects.

HC = healthy controls, SZ = schizophrenia spectrum disorders participants, OT= oxytocin, PL = placebo

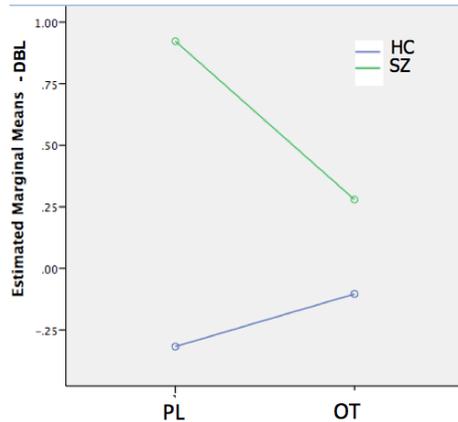
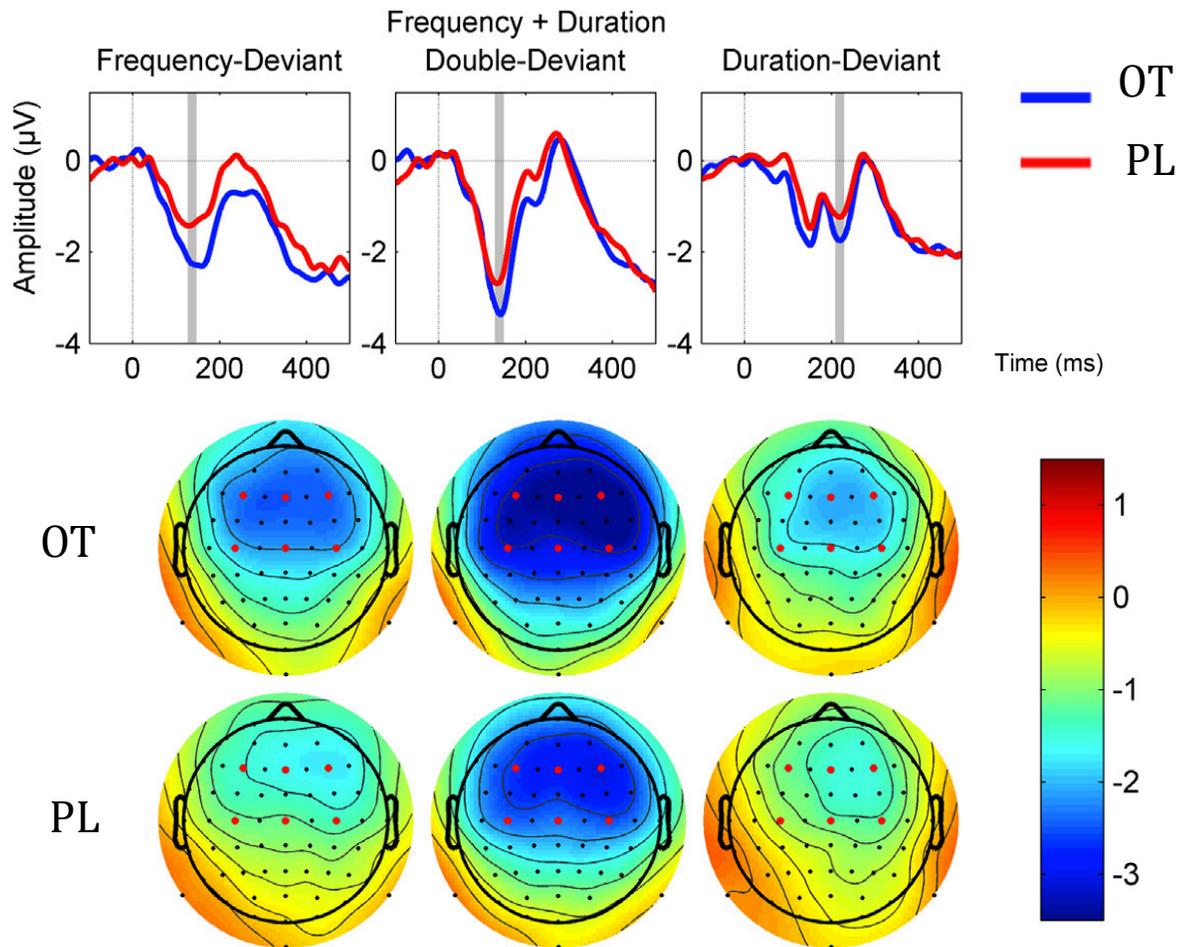


Figure 2. Raw scores for Mismatch negativity (MMN) subjects with in schizophrenia spectrum disorders for each drug and deviant type. Ear-referenced event-related potential (ERP) difference waveforms averaged across frontal sensors for frequency deviant, frequency + duration double-deviant, and duration-deviant are given for each drug (top). The effects of oxytocin (OT) are shown in blue, the effects of placebo (PL) in red. Scalp voltage topography maps of MMN amplitudes are shown for OT (middle) and PL (bottom) for each deviant type. MMN topography maps show the group means of MMN amplitudes around the peak latency ± 10 ms (indicated by gray bars in ERP difference waveform plots). In SZ, OT improves frontal double deviant MMN relative to HC.



4.2. Experimental Paradigm 2: facial emotion processing task

4.2.1. Effects of oxytocin on implicit fear processing: behavioral results

No order effects between the two testing sessions were observed: accuracy and reaction time were not significantly different between sessions. No significant hemifield differences for either accuracy or reaction time were observed.

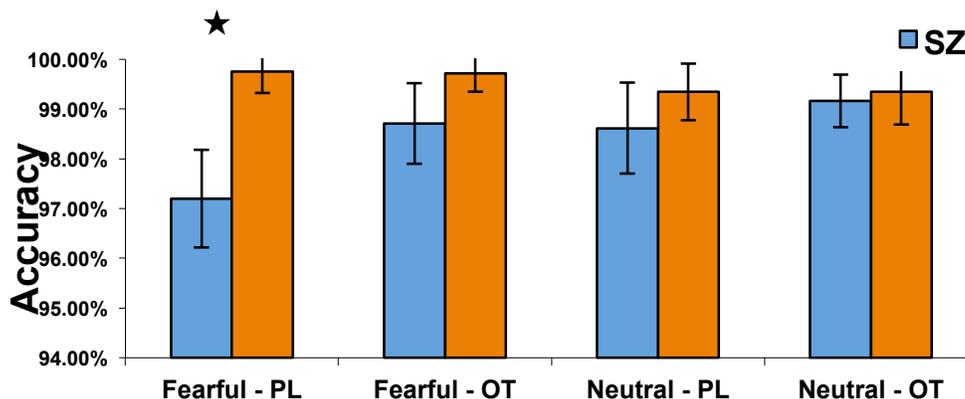
I used independent sample t-test to examine drug-induced between-groups differences in task accuracy and reaction time. Under the effects of placebo, HC were overall more accurate than SZ at discriminating fearful stimuli ($t = -2.575$, $p = 0.015$), but not neutral stimuli ($t = -1.545$, $p = 0.133$). However, the total number of missed trials (late or no responses) was higher for SZ than for HC ($t = 2.309$, $p = 0.030$). When excluding missed trials, SZ showed impairments only in discriminating fearful stimuli ($t = -2.782$; $p = 0.012$). There were no significant differences in RT.

Under the effects of OT, HC are not significantly more accurate than SZ at discriminating fearful and neutral stimuli, with and without taking into account missed trials. There were also no significant differences in terms of missed trials between the two groups. Interestingly, SZ showed a slower RT compared to HC when processing fearful faces at a trend level ($t=1.757$; $p=0.09$).

Next, I used Paired samples T-tests to examine within-group drug-effects in task accuracy and reaction time. The T-test indicated that there were no within-group drug effects for the SZ group in the neutral condition. However, OT improved accuracy for fearful faces in the SZ group, but this improvement does not reach statistical significance ($t= -1.465$, $p= .162$).

Finally, I used a mixed factorial ANOVA with two within-subject factors Drug (OT and PCB) and Condition (fearful and neutral), and one between-subject factor: Group (SZ and HC). The Drug \times Condition \times Group interaction was not significant for accuracy (with and without taking account missed trials), nor for RT.

Figure 3. Effects of placebo (PL) and oxytocin (OT) on the implicit fear processing task. For presentation, means and standard errors are presented.



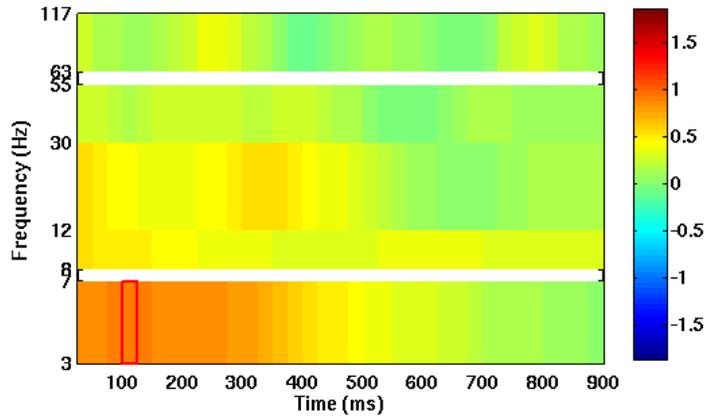
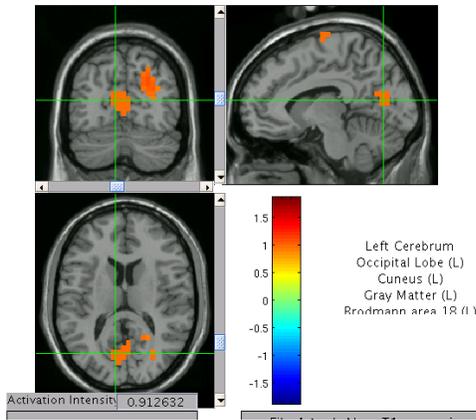
4.2.2. Effects of oxytocin on implicit fear processing: neural results

4.2.2.1. Results from the exploratory time-frequency analysis

The figures displayed hereafter show differences between HC and SZ under placebo in fear-related source-localized activity following a whole brain extraction. MNI coordinates were entered to evaluate time-frequency in specific regions of interest. The contrast is between task trials in which participants passively attended fearful faces vs task trials in which participants attended neutral faces elicited the following significant early activations. For each of these areas, the table reflects the T-map difference values across frequency and time during the trial. More red bars indicate more oscillatory activity for

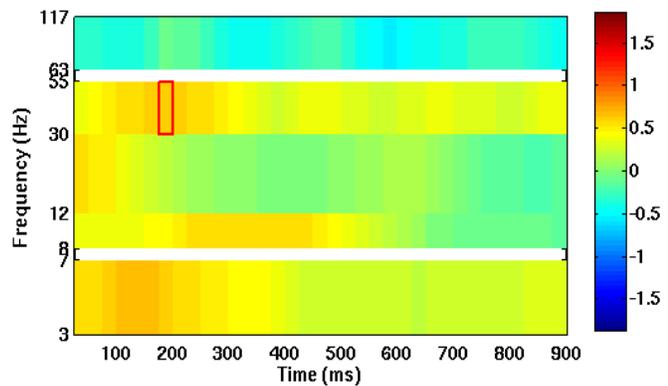
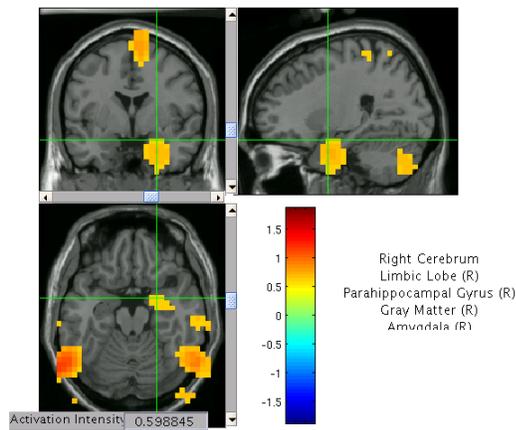
SZ relative to HC, green bars indicate absence of differential activity, blue bars indicate greater activity for HC relative to SZ.

Left Occipital Face Area



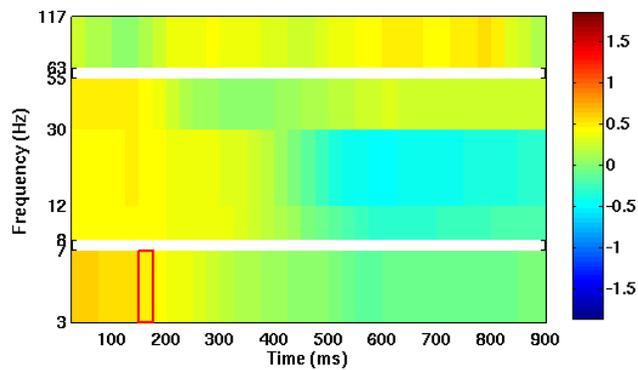
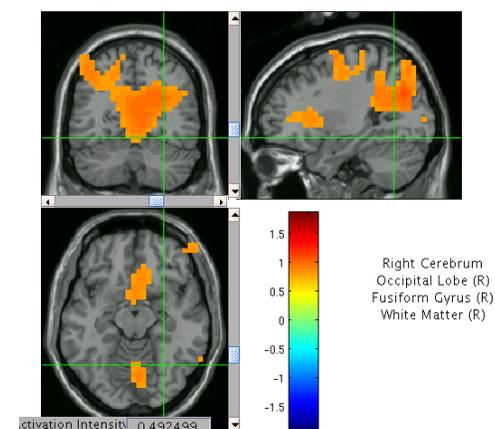
This indicates more theta activity at 100–125 msec in SZ relative to HC.

Right Amygdala



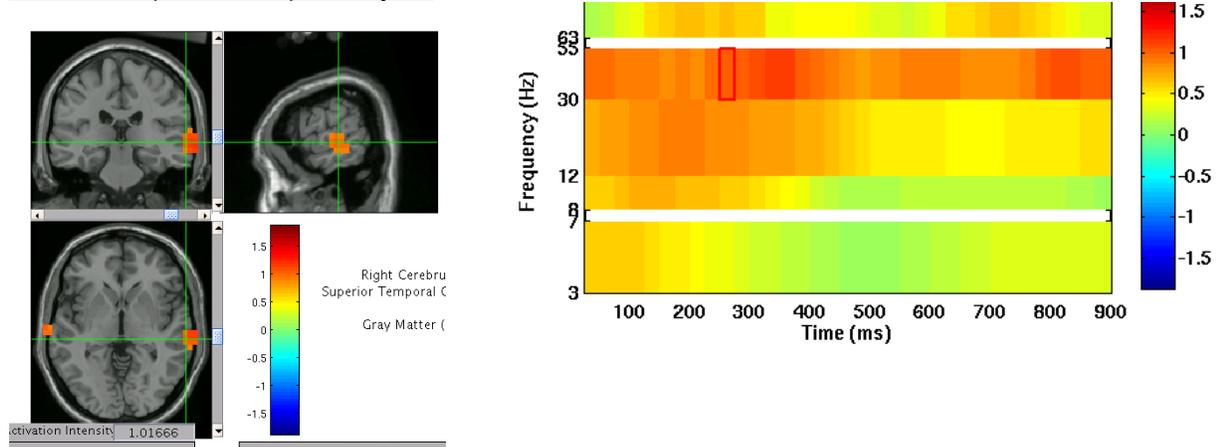
This indicates more theta activity, with peak at 125-150 msec in SZ relative to HC, and more low gamma activity, with peak at 175-200 msec in SZ relative to HC.

Right Fusiform Gyrus



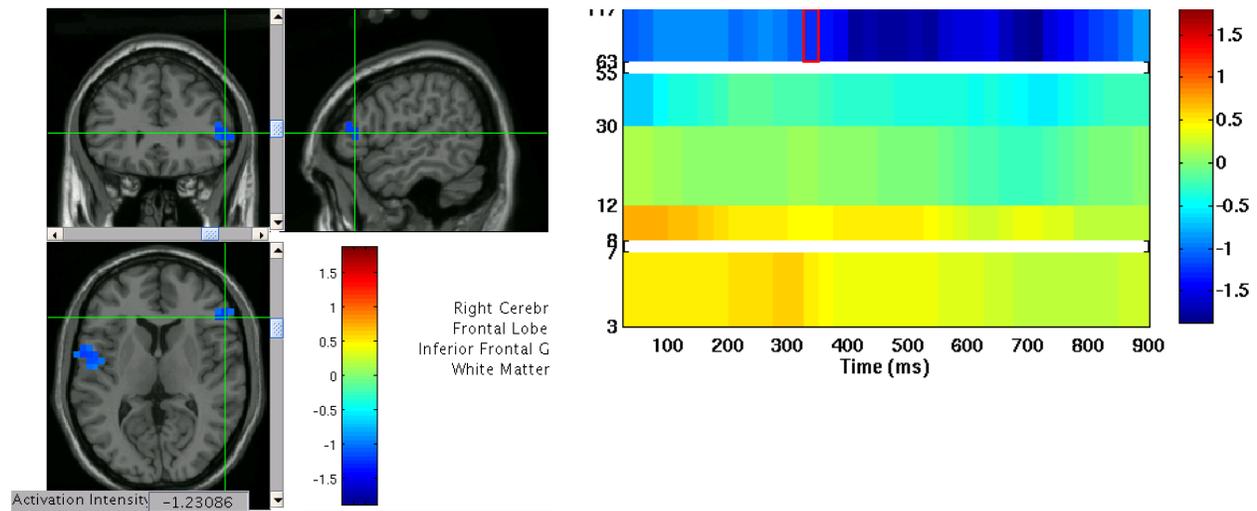
No activity was recorded in the fusiform gyrus using the fearful-neutral contrast. Given its involvement in processing of facial features, the area gets similarly activated during neutral and fearful trials.

Bilateral Superior Temporal Gyrus



This indicates more low gamma activity at 250-300 msec in SZ relative to HC bilaterally.

Right inferior Frontal Gyrus



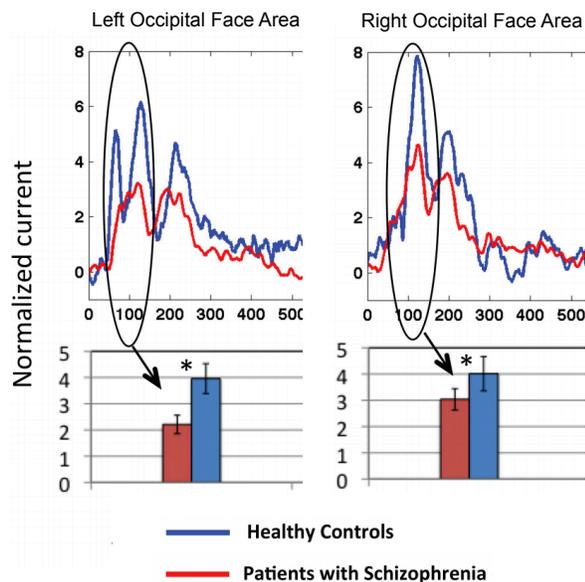
This indicates less high gamma activity with peak at 325-350 msec in SZ relative to HC.

4.2.2.2. Results from the time-locked analysis in regions of Interest

Occipital Face Area. In SZ under placebo, the left occipital face area (OFA) showed more theta activity at 100–125 msec. I therefore decided to extract broadband activity from this area in both hemispheres (MNI Left [-45, -75, 11], Right [-45, -73, 14]) at each time point during fearful trials. I calculated the induced oscillatory activity within the time series data for each trial. Next, I localized trial-by-trial time series and averaged them across trials for each subject. These averages were z-normalized. The

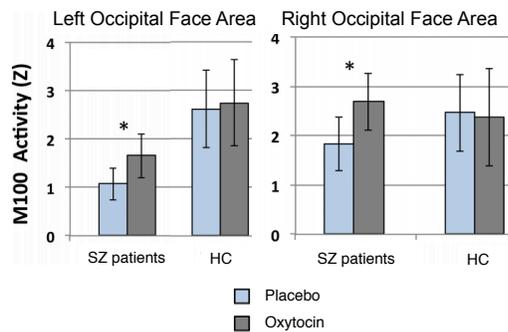
peak of differential activation from the time-frequency analysis was reported around 100–125 msec. To confirm this, I analyzed the maximum z-amplitude from 0 to 250 msec across hemisphere and group. The latency identified from each individual time series, and the latency identified in the across-groupxhemisphere grandaverage time series indicated that the maximal latency obtained in the broadband response at OFA occurred consistently between 50 and 150 msec. Therefore, I averaged amplitude from 50–150 msec post-stimulus-onset and use this metric as a proxy of optimal latency (M100). Under placebo, activity within OFA revealed reduced M100 amplitude in SZ relative to HC (Group: $F[1,49] = 6.24, P = .016$). No significant differences between hemispheres were observed. See Figure 4 for details.

Figure 4. Activity estimated from left and right OFA shows reduced sensory response in patients with schizophrenia spectrum disorders (red) relative to healthy controls (blue) under placebo. For presentation, means and standard errors are presented.



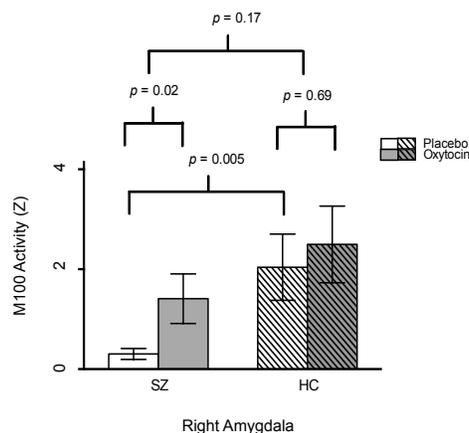
The M100 response in OFA changed differentially in each group depending on the drug (Group x Drug: $F[2,49] = 4.34, P = .019$). Under the effects of OT, the SZ group showed increased M100 (Drug: ($F[1,24] = 8.881, P = .008$), while HC did not: $F[1,24] = .003, P = .96$). There were no significant effects of Hemisphere on the Group x Drug interaction. See Figure 5 for details.

Figure 5. Oxytocin-induced changes in M100 response in the OFA. Broadband M100 response within OFA is increased in SZ subjects under the effects of oxytocin. Healthy controls showed no effects of OT on M100 response. For presentation, means and standard errors are presented.



Right amygdala. The exploratory time-frequency analysis suggested that healthy controls showed less theta oscillations in the right amygdala during the presentation of fearful faces between 100 and 200 msec. Similarly to the process operationalized for the OFA, I decided to extract broadband activity from the right amygdala (MNI Right [21, -1, -22]) at each time point during fearful trials, to average trial-by-trial time series, and to analyze the maximum z-amplitude for the right amygdala. The maximal latency identified from each individual time series and across groups occurred consistently between 150ms and 200 ms post stimulus onset. I therefore average amplitudes from these time windows and call this metric the M100 response for the amygdala. Next, I used repeated-measures ANOVA with Drug (Oxytocin, Placebo) as a within subject factor, and Diagnosis (Healthy, Patient) as a between subject factor. The Group x Drug was non significant ($F[2,49] = 3.02, P = .17$). Under placebo, M100 amplitude in the right amygdala was reduced in SZ relative to HC (Group: $F[1,49] = 7.01, P = .005$). Under the effects of OT, the SZ group showed increased M100 (Drug: ($F[1,24] = 7.553, P = .002$), while HC did not: $F[1,24] = 1.136, P = .69$).

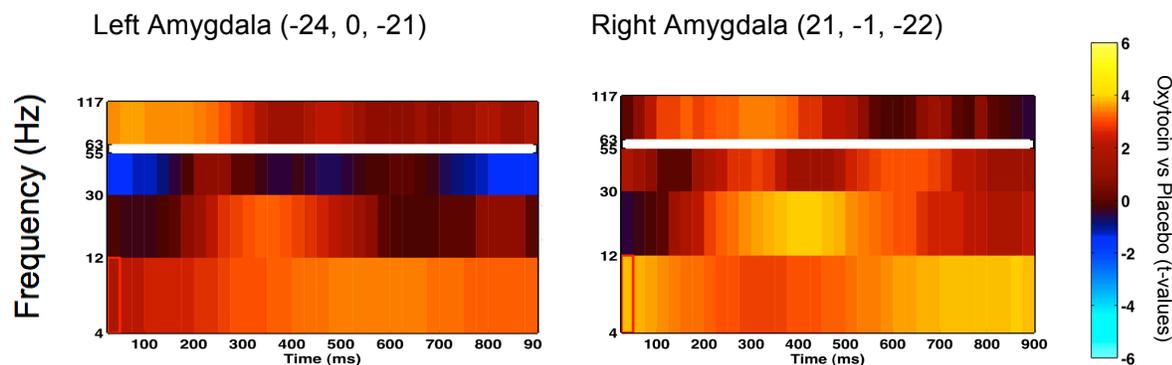
Figure 6. Oxytocin-induced changes in M100 response in the right amygdala. M100 is significantly increased in SZ subjects under the effects of oxytocin. Healthy controls showed no significant effects of OT on M100 response. For presentation, means and standard errors are presented.



4.2.2.3. A better characterization of oxytocin effects on neural oscillations in the right amygdala

Finally, given the evidence of more theta oscillations in SZ relative to HC under placebo in the right amygdala, I was interested in further characterizing the effects of OT on neural oscillations in SZ. The time-locked analysis averages neural activity across trials, presenting averaged time series of the ROI. In this analysis, I decided to use again time frequency analysis to include the intra-individual variability across trials (instead of the average), and submit that to group analyses. I created the contrast between fearful and neutral trials, and used SnPM between-drug paired tests to evaluate differences between the effects of placebo and OT in SZ in terms of early activations in the amygdalae within the 4 frequency bands. I obtained a pseudo-t statistic at each voxel and time window for each frequency band, with t distributions created from 10,000 permutations of the voxel labels. To reduce false positive results, I applied a spatial threshold of 20 contiguous voxels showing activity at 2-tailed t-values corresponding to $p < .05$ prior to querying t-maps for foci of peak activity in they amygdalae. Finally, I translated the foci t-values to p-values to determine and report the actual levels of significance. I display below the tables reflecting T-map difference values across frequency and time during the trial, for the right and the left amygdala. More yellow bars indicate less oscillatory activity for OT relative to PL, red bars indicate absence of differential activity, blue bars indicate more oscillatory activity for PL relative to OT.

Figure 7. T-map difference values across frequency and time during the trial in the amygdalae. Power change in alpha/theta activity occurred in patients with SZ on the OT day in the right amygdala (Contrast is Oxytocin-Placebo in SZ subjects).

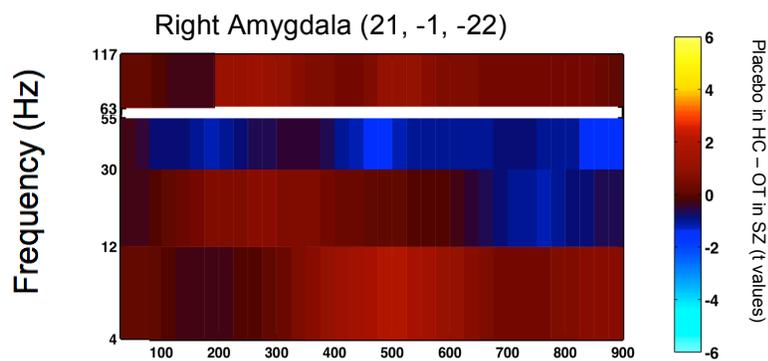


This confirmatory analysis supports OT-induced increases in M100 in the right amygdala, revealing reduced early alpha/theta oscillatory under the effect of OT, within 1cm of *a priori* coordinates. The difference in response was active from 25 to 150 msec, with a peak difference at 25 msec (peak $t[24]$

= 2.095, $P = .03$). In the left amygdala, there were no significant substance-induced T-map difference values in the alpha/theta band across time during the trial.

Finally, I wanted to verify test whether OT had normalized neural oscillations in SZ patients. To this purpose, I conducted a confirmatory time frequency analysis on the right amygdala and used SnPM between group unpaired tests to evaluate differences between SZ under OT and HC under placebo. The data processing is consistent with the one described earlier. The table reflecting T-map difference values across frequency and time during the trial. More yellow bars indicate greater oscillatory activity for HC-PL relative to SZ-OT, red bars indicate absence of differential oscillatory activity, blue bars indicate more oscillatory activity for SZ-OT relative to HC-PL. The absence of between-group power changes in the alpha/theta band from 0 to 200 ms indicate that OT has normalized low-frequency neural oscillations in this time window.

Figure 8. T-map difference values across frequency and time during the trial in the right amygdala. Oxytocin-induced power reduction in alpha/ theta activity in patients with SZ make their alpha/theta activity comparable to those of HC under placebo (Contrast is Placebo in HC subjects – Oxytocin in SZ subjects)



5. DISCUSSION

As patients with schizophrenia spectrum disorders struggle with impairments of social cognition and behavior, which are known to cause an early deterioration of social functioning, it is critical to identify and study pharmacological agents that can effectively target the neural underpinnings of these impairments in order to improve functioning and wellbeing in this population.

Oxytocin appears to be an excellent candidate for a number of reasons. First, it induces reliable behavioral effects on numerous aspects of social cognition and behavior in healthy and clinical populations, including patients with schizophrenia spectrum disorders. Second, neuroimaging research has identified in healthy subjects a distributed network of brain regions that are enriched for OT receptors, are activated by the administration of OT, and finally have shown disturbances in terms of activity and connectivity in patients with schizophrenia spectrum disorders. These network includes cortical and subcortical areas such as the sensory cortices, the amygdala, fusiform gyrus, the anterior cingulate and several other prefrontal and temporal areas. Third, animal studies have suggested the mechanism by which OT affects activity in these circuits, i.e. a transient reorganization of excitatory and inhibitory inputs that reduces/modulates synaptic inhibition and enables long-term synaptic plasticity.

There is already a large body of evidence that shows that exogenous OT improves processing of social and emotional stimuli in patients with schizophrenia spectrum disorders. However, in order to implement the dissemination of OT as a pharmacological treatment, more knowledge is needed to elucidate the neural mechanisms by which OT induces these effects. Therefore, in this study I used Magnetoencephalography Imaging (MEG-I) to evaluate the basic neurophysiological mechanisms of OT effects in patients with schizophrenia spectrum disorders and healthy controls, focusing on early sensory processing, as this is the first step in the cascade of information processing that is known to be impaired in patients with schizophrenia spectrum disorders and responsible for higher order social cognition and behavior deficits.

5.1. Principal results of the mismatch negativity paradigm

The first experimental paradigm examined the effects of OT on auditory mismatch negativity, a sensitive readout of automatic auditory deviance processing that is known to be impaired in schizophrenia spectrum disorders. First of all, the analysis confirmed the presence of frontal double-deviant MMN deficits in patients with schizophrenia spectrum disorders relative to healthy controls under placebo. This is in line with recent studies conducted in samples of patients with

schizophrenia[50, 75] and confirms that combining deviance features in a single stimulus has greater sensitivity to schizophrenia than stimuli that are deviant in only a single feature[78]. More importantly, OT was found to increase the amplitude of DBL MMN in patients with schizophrenia spectrum disorders relative to placebo. This is in contrast with finding from an old study conducted by Born and colleagues that had found no differences in MMN after OT administration. However, the Born study administered 24 and not 40 IU of OT, had a smaller sample size, and used a single deviant paradigm, and not a double deviant. Although preliminary in nature, these results have far reaching implications: as MMN is elicited pre-attentively and does not include any social element, MMN improvements induced by OT suggest that OT targets information processing at its earliest stages. While these findings do not offer per se an explanatory model for the observed MMN improvements, results from a recent animal provide an interesting framework. Mitre and colleagues found in fact that OT modulates synaptic inhibition in the left auditory cortex and enables synaptic plasticity. As MMN is considered an index of experience-dependent synaptic plasticity in the service of auditory sensory/perceptual learning[53], it is possible that OT improves MMN by enabling synaptic plasticity. Further, given that MMN depends critically on *N*-methyl-D-aspartate receptor (NMDAR) function[43], and NMDAR hypofunction is a mechanism underlying plasticity deficits in schizophrenia spectrum disorders[52], it is possible that the mechanism by which OT improves synaptic plasticity is NMDA-R mediated. Recent evidence from another animal study supports this hypothesis, showing that the activation of the presynaptic OT receptor increases glutamate release[174]. While more studies are obviously needed to elucidate whether the administration of OT remediates the NMDA-R hypofunction present in schizophrenia spectrum disorders, this hypothesis could also explain why healthy controls in this study do not show MMN changes after OT administration. In the absence of NMDA-R hypofunction, synaptic plasticity in healthy controls may be intact, and therefore not affected by OT administration. Speculations aside, to my knowledge this is the first study that proves that OT alters a non-social neurophysiological index of elemental auditory information processing. If replicated in the auditory domain and possibly extended to other sensory modalities[175], this set of findings would revive the hypothesis that OT exerts effects on very elemental levels of information processing, above and beyond the well known effects on social cognition.

5.2. Principal results of the facial emotion processing paradigm

The second experimental paradigm examined the effects of OT on facial emotion processing, another stage of information processing that is disrupted in schizophrenia spectrum disorders and drives deficits in social cognition and behavior. In particular, the paradigm evaluated the behavioral and neural responses evoked by fearful faces compared to neutral faces.

It is important to clarify that behavioral effects were not the primary outcome of this analysis. The implicit fear processing task was adapted and implemented in the paradigm because of its previously established ability to elicit MEG-detectable activity in regions of interest, including the amygdala, the fusiform gyrus and the dACC[86]. In other words, the task was included in the study to elicit neural effects and not to demonstrate behavioral changes between OT and placebo.

Still, we report here results from the behavioral analysis. Under placebo patients with schizophrenia spectrum disorders are significantly less accurate than HC at discriminating fearful faces, but not neutral faces. Given the implicit nature of the task, participants were instructed to selectively target the scrambled patterns and push the correspondent button, so that all faces (neutral and fearful) were attended passively. The fact that patients with schizophrenia spectrum disorders made more mistakes in choosing the scrambled patterns in trials where fearful faces were presented may suggest an attention bias toward threatening stimuli, a phenotype that is well demonstrated in schizophrenia[176]. In schizophrenia spectrum disorders patients, I also found a trend for OT to improve accuracy for fearful faces, but not for neutral faces. The lack of drug-induced differential effects in terms of accuracy for the neutral condition could be justified by ceiling effects. Indeed, individuals with SZ showed accuracy rates for the neutral condition higher than 98%. Ceiling effects could also explain the lack of significant differences in accuracy in HC between the placebo and OT conditions both for neutral and fearful trials, where HC uniformly performed with accuracy above 99%. It is important to note that the level of difficulty was kept low in order to increase the number of trials that could be computed into the MEG analysis. Changes in oscillatory power are in fact more easily identifiable with a larger number of trials, in stimulus-locked time frequency analyses, especially when the regions of interest are subcortical structures, like the amygdala.

5.2.1. TFA provided high-impact data on dysfunctional oscillatory patterns underlying facial emotion processing in schizophrenia spectrum disorders

The exploratory time frequency analysis investigated differences between HC and SZ under placebo in fear-related source-localized activity following a whole brain extraction. Compared to healthy controls, patients with schizophrenia spectrum disorders showed abnormal neural oscillations in several frequency bands across various brain regions. In particular, increased theta activity was found at 100-125 ms in the left OFA and at 125-150 ms in the right amygdala. More low gamma activity was found at 175-200 ms in the right amygdala and at 250-300 ms in the bilateral STG. Less high gamma oscillations were found in the right IFG at 325-350 ms. Notably, no differential activity was found in the right fusiform gyrus or in the left amygdala.

Fear-related differential activity between HC and SZ was observed in areas where previous fMRI and MEG studies found activity during facial emotion processing tasks[80, 81, 84, 86, 87, 91, 165, 167, 177]. Besides consolidating evidence about the neural network underlying facial recognition, these TFA findings provide two important sets of information: the temporal patterns of activation in this network, and a better characterization of which neural oscillations are impaired in each node.

Regarding the temporal patterns of activation, it is arguable that delayed processing of social information in any of these networks nodes could underpin the impairments in facial emotion recognition that characterize schizophrenia spectrum disorders. In other words, disturbances of the neural network may not only be related to aberrant activity, as indicated by impaired oscillations, but also to inefficient timing. Findings from this TFA however seem to suggest that the timing of activation patterns in schizophrenia spectrum disorders is not impaired, with the primary sensory cortex and the amygdala responding very early (around 100 ms) and higher order associative areas getting activated later on (250-350 ms). This is entirely in line with what is previously described in the literature on facial emotion processing[80, 81, 84, 86, 87, 91, 165, 167, 177].

Regarding the neural oscillations, findings from the TFA shed new light on which frequency bands are driving impairments of facial emotion processing in schizophrenia spectrum disorders. Neural oscillations are considered an assembly of extracellular local field potentials (action potentials) representing synchronous activity of a large set of neurons or neural circuits. Scalp-recorded oscillations measure synchronization of activities directly or indirectly reflecting neural communication processes. A general principle of the functional role of oscillations in various frequency bands is that because of conduction delays in the brain, slow oscillations are able to travel further distances and link remote areas of the brain. Fast oscillations such as gamma are in general less capable to traverse large distances and are therefore more likely to be restricted to local circuits. Patients with schizophrenia spectrum disorders are known to exhibit impaired neural oscillatory activities during sensory and cognitive tasks. Abnormalities of neural oscillations are found essentially in all frequency bands in schizophrenia spectrum disorders patients in a number of tasks.

Many recent electrophysiological studies of schizophrenia spectrum disorders have focused on high frequency oscillations at gamma band because of its critical role in cognitive functions. Gamma wave is a pattern of neural oscillation in humans with a frequency between 25 and 100 Hz. Cortical oscillations in the frequency range of 30–90 Hz—so called gamma band oscillations—can be recorded from a wide range of brain regions during rest or the performance of cognitive-motor tasks, and are assumed to reflect wide-scale neuronal processes associated with cognition and perception. Event-related gamma responses greater than 60 Hz (High Gamma), extending up to approximately 200 Hz, have been observed in a variety of functional brain systems. Preliminary studies suggest that high gamma oscillations occur at latencies consistent with the timing of task performance. Such oscillations

are variably time-locked to specific sensory or motor events. It has been proposed that gamma oscillations generally reflect local intracortical activity. Thus, high-frequency, narrowly tuned gamma oscillations are elicited by many types of processes. As mentioned above, recent research supports the evidence of a gamma band dysfunction. Reduced gamma band power and synchronization are reported in schizophrenia spectrum disorders in steady state, sensory gating, arithmetic task, speech, oddball, Gestalt perception, and working memory conditions. However, inconsistent and opposite findings exist. Increased gamma has been described under working memory, somatosensory stimulation, visual recognition tasks, and unmedicated conditions in schizophrenia spectrum disorders. Higher gamma synchrony is correlated with more severe psychotic symptoms or the opposite. The question of whether there is a “gamma band reduction in schizophrenia” becomes a prominent question by itself. Available evidence appears to suggest that there are gamma band reductions during impaired cognitive functions but sometimes no abnormalities or even increased gamma band activities at rest or during less cognitively demanding conditions[178].

While evidence of increased gamma activity was found at 175-200 ms in the right amygdala and at 250-300 ms in the bilateral STG (which is challenging to interpret, given the controversy on the role of gamma waves in schizophrenia – see above), results of increased theta activity at 100-125 ms in the left OFA, and at 125-150 ms in the right amygdala definitely deserve more attention. Increased theta/delta is one of the more consistent observations in schizophrenia EEG/ERP studies, which occurs locally and globally, in unmedicated, in first episode, and in chronic patients with schizophrenia. Additionally, less suppression of the alpha-theta activities is the most significant oscillatory component marking the genetic liability for schizophrenia during sensory gating. Finally, a recent review of MEG studies of spontaneous activity revealed converging evidence of increased theta and delta oscillations in subjects with schizophrenia. Like other frequencies, contradictory and negative findings exist, but taken together these findings indicated that oscillatory abnormalities in schizophrenia not only interest gamma reduction but also include slow frequencies. In particular, the evidence of increased theta activity in schizophrenia spectrum disorders seems solid. **Early increased delta oscillatory activity in the right amygdala and the left OFA could therefore represent one of the critical mechanisms responsible for impairments of facial emotion processing in schizophrenia spectrum disorders.**

This explanatory model is further complicated by the fact that frequency bands do not occur as distinct phenomena. Low frequency oscillations may provide an essential role in engaging gamma rhythms and determining their behavioral consequence in attention. Another important aspect is their cross-frequency communications. Cross-frequency coupling refers to interactions between oscillations of different frequency bands. The most well studied example is the observation of gamma frequency engagement in certain phases of theta cycles (theta-gamma coupling). Emerging evidence of theta-

gamma coupling has also been demonstrated in humans but has not yet been related to schizophrenia spectrum disorders, although it has been proposed. Indeed, in humans, Canolty et al found that across a wide range of tasks, gamma and theta oscillations interacted such that the amplitude of high gamma oscillations (80–150 Hz) was increased at the trough of theta oscillations. One intriguing study in support of this hypothesis used intracranial recordings in the hippocampus of humans during a working memory task. Theta oscillation slowing was observed as the number of items to be remembered increased, allowing more gamma cycles to occur in each theta phase. Because working memory impairment is one of the core deficits in schizophrenia spectrum disorders, abnormal theta-gamma coupling, which has been linked to successful memory in humans, could be a contributing factor and warrants further investigation. It is possible that the observed increased theta in the right amygdala and left OFA may compromise theta-gamma coupling and therefore negatively affect processing of facial emotions. More studies are needed to test this hypothesis.

5.2.2. Tentative explanations for the fear-related increase in theta oscillatory activity in the right amygdala and in the left occipital face area

The right amygdala is well known for its role in early detection of fear in the context of implicit facial emotion processing. The majority of the fMRI studies evaluating activation patterns of the amygdala in response to fearful faces in schizophrenia show that patients have abnormally increased and sustained amygdala activation when viewing fearful faces relative to low-level baselines. Other studies show that schizophrenia patients exhibit an initial increased right amygdala response to all faces (irrespective of emotional connotations), and that this high initial amygdala responsivity to facial expressions at an automatic processing level substantially decreases with time. Some authors have also postulated that this amygdala deactivation over time might reflect an automatic mechanism by which schizophrenia patients suppress the processing of facial stimuli. Recent MEG studies in HC have reported increases in gamma-band synchronization in the amygdala related to processing emotional stimuli at early latencies between 20 and 170 ms. Additionally, Hung found in healthy controls that the right amygdala showed increased activity when viewing fearful faces around 100 ms and also exhibited temporally dissociated activations to input, suggesting early subcortical versus later cortical processing of fear. In this study, we find evidence of increased theta activity in SZ. Given the nature of the contrast used in the TFA (fearful trials vs neutral trials), it is not possible to determine whether this increased theta activity is attributable to an increase in theta driven by fearful trials or to a decrease of theta driven by neutral trials. Nonetheless, I believe that the most conservative explanation for this finding is that fearful trials induce early arousal by threat signals from the eye region, which in turn intensifies theta activity.

More challenging is to find an explanation for the fear-related activity in the left OFA. The OFA is the first stage in the distributed network for face perception that specifically represents the parts of the face such as the eyes and the mouth. Neural oscillations in this region should not be affected by the emotional connotations of faces.

However, some authors have postulated that the OFA has sensitivity to facial emotions, similarly to the fusiform gyrus. In the Hung study conducted on healthy controls, the right fusiform showed greater activation in response to all fearful compared to all neutral faces at 170 ms. This is consistent with previous ERP results where fearful faces produced the largest and longest latency N170s. In the same MEG study, the time course in the right fusiform showed higher activity to fearful faces at 170 ms, later than the peak response to all faces at 150 ms, suggesting that the emotional component may be differentially processed later in face perception. It has been argued that this delay in the M/N170 to fearful faces is due to incorporation of feedback from the rapid earlier processing for highly salient stimuli. Similarly it is possible that earlier processing of fear in amygdalar regions may provide feedback and influence the response of the OFA. If this justifies potentially the presence of activity with the contrast neutral/fearful, it does not provide explanation for why SZ and HC showed differential activity in the TFA. One hypothesis, consistent with what has been presented for the amygdala, is that increased theta activity in the amygdala of SZ patients induces increased in theta activity in the OFA. More studies are needed to test rigorously these hypotheses.

5.2.3. The time-locked analysis provided insight on the effects of oxytocin on M100 evoked potentials

One significant problem of exploratory TFAs is that they use contrasts to identify condition-related differential activity. In this study, the contrast was between source localized activity during task trials in which participants passively attended fearful faces vs task trials in which participants attended neutral faces. Therefore, it is not possible to determine whether increased theta activity in right amygdala and left OFA in SZ compared to HC is due to an increased theta activity during fearful trials for SZ or to a decreased theta activity during neutral trials for SZ.

The time-locked analysis permitted to address this issue by analyzing exclusively fearful trials and comparing the activity they evoked between SZ and HC. Compared to HC, M100 in SZ was reduced in the left OFA, and to a lesser extent, in the right OFA (although the differences between hemispheres were not significant), and in the right amygdala. The reduced M100 response observed in SZ compared to HC in sensory cortices and the amygdala (a finding that is consistent with weaker M100/N100 responses in patients with schizophrenia reported in the literature[86, 86, 179–181]) seems to be the associated with aberrant increased theta oscillations in these regions. This suggests

that increased theta oscillations during fearful trials in these areas could impede the assembly of an adequate M100 response.

But what are the effects of OT on these early abnormal neural responses?

The time-locked analysis for the right and left OFA showed that OT significantly increased M100 in patients with SZ, without significant effects of hemisphere. Interestingly, healthy controls showed no effects of OT on M100 response. Similarly, OT increased M100 in the right amygdala, but did not induce any effects in healthy controls. This pattern of results closely resembles – and nicely complements - what was observed in the auditory MMN paradigm: OT improves early neural responses to implicit fear-related information processing in areas that are known to be disrupted in SZ and to underpin facial emotion recognition deficits.

As this is the first MEG study investigating the effects of OT in any patient population, findings from this study are here compared to previous fMRI studies. Many fMRI experiments investigated the effects of OT on the amygdala in healthy controls. It is at this point clear that the effects of OT are extremely context-dependent: the emotional valence of the stimuli, the sex of the participants, the implicit or explicit processing of stimuli are factors all known to modulate the effects of OT. As an example, Domes showed that in women OT enhanced the BOLD signal in the left amygdala, the fusiform gyrus and the superior temporal gyrus in response to fearful faces and in the inferior frontal gyrus in response to angry and happy faces following OT treatment. This effect was independent of fixation pattern to specific sections of the facial stimuli as revealed by eye tracking. While involving the same neural network, these results are at odds with the previously reported effects found in men[158]. Additionally, different amygdala subregions respond differently to OT, and MEG unfortunately does not have the sufficient spatial resolution to study these subregions separately. Finally, there is a limitation dictated by the timing of activation in the amygdala, with fMRI studies providing limited information on when the amygdala get activated and what other brain areas are influencing this activation. The only fMRI study conducted in SZ found that OT decreased amygdala reactivity to fearful faces attended passively[145], although the sample size was very small and 24 IU of OT were used instead of 40 IU. Recent findings from electrophysiology and multimodal neuroimaging have elucidated the relationship between patterns of cortical oscillations evident in EEG/MEG and the functional brain networks evident in the FMRI BOLD signal. If prior literature has suggested that high-frequency cortical oscillations coordinate neural activity locally, while low-frequency oscillations coordinate activity between more distant brain regions, in actuality low- and high-frequency work in concert, coordinating neural activity into whole-brain functional networks. When relating such networks to the fMRI BOLD signal, the patterns of cortical oscillations change at the same speed as cognitive states, which often last less than a second. Consequently, the slower BOLD signal may often reflect the summed neural activity of several transient network configurations.

Therefore, it is quite challenging to directly compare the amygdala hyper/hypoactivity with the observed M100 enhancement. Pragmatically, findings from this study provide another neurophysiological index that is known to be impaired in SZ and improved by OT administration, and can therefore be used to better elucidate the effects that OT exerts on early sensory processing and other cognitive processes.

It is noteworthy to mention that, similarly to the MMN paradigm, OT does not seem to impact M100 evoked potentials in the right amygdala or in the bilateral OFA for healthy controls. Whereas a large body of evidence suggests that M100 is not a static biophysical measure, but rather a dynamic index of the status of a network that can be modified by selective attention, pharmacological agents and cognitive interventions[179, 182], in our study OT did not manage to induce a significant change. It is important to keep in mind the great deal of inter-individual heterogeneity observed for M100 responses in OFA and the right amygdala, as shown by the standard errors depicted in Figures 5 and 6 of Chapter 5.

5.2.4. A confirmatory time-frequency analysis shows that oxytocin normalizes aberrant early alpha/theta oscillations in schizophrenia spectrum disorders

In order to quantify and allow for the comparison of early sensory response across drugs and samples, the time-locked analysis averages neural activity across trials for each individual and each condition (neutral/fearful). The averages time series may obscure some of the unique effects that OT induces in specific frequency band at specific time points.

I therefore utilized TFA again to conduct a between drug test and study in greater detail the effects of OT in the amygdala of patients with schizophrenia spectrum disorders across frequency and time. The analysis revealed important information: the increased theta oscillatory activity that was present in the right amygdala between 100 ms and 200 ms with peak at 125-150 ms under placebo is significantly attenuated by OT. As shown in Figure 7 of Chapter 5, OT effects are largely evident on low-frequency oscillations, with a significant reduction between 25 and 150 ms of alpha/theta activity, and a later reduction of beta between 300 and 500 ms. The limited spatial resolution of MEG for subcortical structures offers this information within 1cm of a priori coordinates. It is possible that different subregions of the amygdala respond differently to the effects of OT. In particular, the peak difference in response between OT and placebo was recorded at 25 ms. The left amygdala serves in this context as an excellent control condition that shows the context-dependent effects of OT. First, in the exploratory TFA there was absence of differential activity in the left amygdala between SZ and HC, as this area is specifically activated by the explicit (and not implicit) processing of fearful stimuli, and was also found to be not activated in the MEG study the task was adapted from[86]. Now, in this

confirmatory TFA on the effects of OT, there are no significant T-map differences values across frequency and time between OT and placebo, suggesting that if the brain region is not solicited by the task, the administration of OT does not modify the oscillatory patterns. The last segment of the confirmatory TFA attempted to compare directly the neural oscillations in patients with SZ under the effects of OT and those of HC under the effects of placebo. The explicit goal was to see whether the mitigation of alpha/theta oscillatory activity induced by OT in SZ normalized functioning in the right amygdala. No significant between-group changes in oscillatory power were observed in the alpha/theta band (and in the high gamma band) during the trial. Even though absence of significant differences does not automatically imply homogeneity of neural oscillatory activity, this constitutes an important proof that OT has normalized low-frequency neural oscillations in SZ, making them similar to those of HC under placebo.

5.3. Limitations

First and foremost, the literature review, the experimental paradigms and the interpretation of results are centered around the psychophysiology of schizophrenia. In the sample recruited for the study, only 60% met the diagnostic criteria for schizophrenia, while 28% met criteria for schizoaffective disorder, and 12% for bipolar disorder with psychotic features. In these analyses, I did not control for diagnosis and conducted analyses on the whole sample. This choice is justified by the fact that the diagnostic categorization of schizophrenia, schizoaffective and bipolar disorders has been recently questioned (see introduction) and dimension-focused trans-diagnostic approaches represent today the major NIMH guideline for research projects conducted on psychosis.

Some of the studies cited in the dissertation, especially those conducted before the NIMH RDoC initiative, collected data from samples of patients with schizophrenia, explicitly excluding subjects with other psychotic disorders. Recent efforts have been made by the scientific community to demonstrate intermediate phenotypes of dysfunction in people with schizoaffective disorder and bipolar disorder with psychosis. For example, most behavioral studies that investigated the effects of oxytocin in psychotic populations recruited subjects with schizophrenia and schizoaffective disorders, and, to date, no studies found differences attributable to diagnosis.

Similarly, the neurophysiological abnormalities mentioned in the introduction – disturbances of sensory processing as indexed by MMN, spatially and temporally dysregulated activity in neural nodes responsible for facial emotion processing – have been found in people with schizoaffective disorder and bipolar disorder with psychotic features.

I acknowledge that this is a methodological limitation of the current study that could limit the generalizability of findings. Nonetheless, it reflects current trends in psychiatric research that are influencing the way innovative neuroscientific knowledge is being produced. Given the preliminary

nature of the study and the sample size, there was simply not enough power to detect the influence of different diagnoses on neural activation patterns. Future studies should aim to recruit larger sample of patients to evaluate whether belonging to different illnesses in the psychotic spectrum predicts differential neural activation patterns in response to oxytocin administration.

Another limitation of the study is that contextual subjective experiences of study participants were not evaluated prior and during the experiments. In particular, anxiety and fatigue are known to affect performances on a number of neuropsychological and neuroimaging tasks, and there is the possibility that oxytocin may exert an effect on these psychological states. Although the experiment did not last more than thirty minutes in total, and participants recruited for the study were encouraged to take breaks before and after EEG/MEG recording sessions, it is possible that the data collected on a per-subject basis may be affected by contextual factors. Two elements mitigate the possible detriments of this inattention: first, both experimental paradigms employed hundred of trials to capture strong signals from the neural regions of interest; second, neuroimaging analysis averaged across trials, thereby washing out “contextual noise” that would have affected the quality of the results. Nonetheless, future studies should implement momentary assessments of contextual psychological states and evaluate the effects of oxytocin accordingly.

A third limitation regards the effect that psychopharmacological medications, and specifically second generation antipsychotics and antidepressants, have on MMN. In order to be enrolled in the study, participants had to be taking a single atypical antipsychotic for at least six months with no dosage changes in order to minimize medication confounds. Antidepressants and some atypical antipsychotics have targeted activity on serotonergic receptors, which is known to have an impact on MMN [183, 184]. The heterogeneity of the pharmacological regimens in light of the small sample size did not allow for an in-depth assessment of the effects of serotonergic medications on MMN. Future analyses will evaluate whether there are significant differences in MMN between study participants who were taking serotonergic medications vs those who were not.

The data presented in this dissertation constitute a portion of the planned analyses. More work is needed to re-analyze activity in the right fusiform gyrus, an area that prior research considers critical in the processing of facial features, where the MEG study from which the task was adapted had found increased activity around 170 ms in the contrast fearful/neutral faces in HC[86]. Within-group TFA will help characterize whether this area is sensitive to fearful emotions in patients with SZ.

Fear-related differential activity was found in higher order areas that are known to be implicated in facial emotion processing, like the STG and IFG. Connectivity analysis will be conducted to estimate the role that these areas of later activation plays during facial emotion processing.

Further, we found evidence that OT improves M100 and normalizes early alpha/theta oscillations (25-150 ms) during the processing of fearful emotion. It remains unclear if these two neurophysiological responses are interconnected, and if are specific to threat-related facial emotions.

Finally, the tasks used in the study did not explicitly probe facial affect recognition, the neuropsychological domain that strongly predicts the level of social cognition and social functioning. Therefore, we cannot conclude that the observed neurophysiological improvements determine actual improvements in facial affect recognition. Future experiments will incorporate explicit facial affect recognition tasks and correlate behavioral and neural effects induced by OT. However, a recent study by Kanat conducted in healthy men showed that OT attenuated neural correlates of early arousal by threat signals from the eye region, but did not have any impact on mere emotion detection, suggesting that effects of OT on brain activity are not always attributable to differences in behavioral performance[183].

5.4. Conclusions

In summary, this study provided high-impact data on whole-head oscillatory patterns underlying facial emotion processing in schizophrenia spectrum disorders. Both evoked and induced activity induced by stimulus and experimental contrasts were examined, suggesting a complex pattern of aberrant neural oscillations during the processing of fearful faces in schizophrenia spectrum disorders.

Additionally, the study showed that oxytocin improves measures of early sensory information processing (MMN, M100 in amygdala and OFA), and normalizes abnormal low-frequency neural oscillations in SZ in the right amygdala. This constitutes proof that a single dose of exogenous oxytocin remediates some of the neural abnormalities underlying sensory processing deficits and facial emotion processing deficits in schizophrenia spectrum disorders. To our knowledge, this is the first study demonstrating the influences of intranasal oxytocin on neural correlates of information processing at a very early perceptual stage. The causality within communication pathways between the amygdala, the ventral visual system, the auditory system, and the brain stem and its potential modulation by oxytocin should be explored at different stages of emotion perception. Together, these attempts may increase our understanding of the temporal dynamics underlying oxytocin effects on the cognitive processing of social signals.

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7. CONGRESSES AND SEMINARS, PROCEEDINGS

- 10/2016. Biagianti B. "CLIMB: A Mobile Platform to Treat Social Cognition Impairments and Improve Social Functioning in Psychosis". Oral presentation. IEPA Conference. Milano, IT
- 8/2016. Biagianti B., *et al.* " CLIMB: A Mobile App Intervention to Treat Social Cognition Impairments and Improve Social Functioning in Psychosis" Poster. NIMH Mental Health Services Research Conference. Bethesda, MD.
- 8/2016. Biagianti B., *et al.* " CLIMB: A Mobile App Intervention to Treat Social Cognition Impairments and Improve Social Functioning in Psychosis" Poster. Cognitive Remediation in Psychiatry Conference. NYC, NY.
- 6/2016. Biagianti B. "CLIMB: A Digital Intervention to Treat Social Cognition Impairments and Social Isolation in Chronic Psychosis". Oral presentation. Cognitive Remediation in Psychiatry Conference. NYC, NY.
- 5/2016. Biagianti B., *et al.* "CLIMB: A Mobile app intervention to Treat Social Cognition Impairments in Psychosis". poster. X-tech Conference. SF, CA.
- 4/2016. Biagianti B, *et al.* "CLIMB: A Mobile App Intervention to Treat Social Cognition Impairments and Improve Social Functioning in Chronic Psychosis". Poster. Schizophrenia International Research Society Conference. Florence, IT.
- 4/2016. Biagianti B, *et al.* "Comparing the Efficacy of Two Types of Cognitive Remediation in schizophrenia: Results from a Two-Site Retrospective Cohort Study". Poster. Schizophrenia International Research Society Conference. Florence, IT.

- 3/2016. Biagiante B. "CLIMB: Dissemination of behavioral interventions using mobile platforms". Oral presentation. NAMI San Francisco. SF, CA.
- 3/2016. Biagiante B. "Targeting Sensory Processing Abnormalities in Schizophrenia with cognitive training". Guest Lecture for USF Cognitive Neurotherapeutics advanced seminar. SF, CA.
- 8/2015. Biagiante B. "CLIMB: A mobile intervention for chronic psychosis. Dissemination of behavioral interventions and assessments using mobile platforms". Oral presentation. King's College, London
- 6/2015. Biagiante B, et al. "iPad-based cognitive training for individuals with schizophrenia: results from a pilot pseudo-RCT. Poster. Cognitive Rehabilitation in Psychiatry Conference, NYC, NY.
- 5/2015. Biagiante B, et al. "Using iPads to deliver auditory perceptual training, clinical assessments, and neuropsychological testing to individuals with schizophrenia". Poster. ESCONS Conference, SF, CA.
- 3/2015. Long C, Biagiante B, et al. "Auditory Processing Speed as a Marker for Generalized Cognitive Function in Schizophrenia". Poster. 15th International Congress On Schizophrenia Research. Colorado Springs, CO.
- 3/2015. Biagiante B, et al. "The Moderating Role Of Motivational Deficits On Neurocognitive Functioning Across The Course Of Schizophrenia". Poster. 15th International Congress On Schizophrenia Research. Colorado Springs, CO.
- 1/2015. Jackie DesJardin, Bruno Biagiante, Elena Gasparini, Josh Woolley. "Effects of Oxytocin on Fear-Processing In Schizophrenia". Poster. Rap-tr presentation, UCSF. SF, CA.
- 1/2015. " Treatment of sensory processing abnormalities in schizophrenia spectrum disorders". Oral presentation NAMI-East Bay members Speaker's Meeting. Albany, CA. Presenter
- 9/2014. "Targeting sensory processing abnormalities in schizophrenia". Oral presentation Posit Science Inc. SF, CA Presenter
- 6/2014. Innovation HealthJam: Health Innovations for Vulnerable Populations - World Wide. VIP Speaker.
- 5/2014. Biagiante B, Hinkley LBN, Nagarajan S, Vinogradov S. "Reduced high-frequency neural synchrony in prefrontal regions during implicit learning in individuals with schizophrenia." Poster. UCSF Department of Psychiatry 11th Research Retreat. SF, CA.
- 4/2014. Biagiante B, Hinkley LBN, Vinogradov S, Nagarajan S. "Impoverished High-Frequency Oscillatory Activity in Frontal Cortex in Individuals with Schizophrenia during Implicit Sequence Learning". Poster. Schizophrenia International Research Society Conference. Florence, IT.
- 4/2014. Vinogradov S, Subramaniam K, Biagiante B, Hooker C, Fisher M. "Combining cognitive and social cognitive training for individuals with Schizophrenia". Oral presentation. Schizophrenia International Research Society Conference. Florence, IT.

- 3/2014. Biagiante B, Woolley J. "ipad-based remote cognitive training for individuals with schizophrenia". Oral presentation. Digital Mental Health Innovations at UCSF. San Francisco, CA.

8. PUBLICATIONS

1. **Biagiante B, et al.** Auditory mismatch negativity impairments predict response to auditory training in early illness schizophrenia-spectrum patients. *Biological Psychiatry*(2016). *Under Review*.
2. Woolley J, ..., **Biagiante B, et al.** Intranasal oxytocin increases facial expressivity, but not ratings of trustworthiness, in patients with schizophrenia and healthy controls. *Psychological Medicine* (2017).
3. **Biagiante B, et al.** Creating Live Interactions to Mitigate Barriers (CLIMB): A Mobile Intervention to Improve Social Functioning in People With Chronic Psychotic Disorders. *JMIR Ment Health*. (2016).
4. **Biagiante B, et al.** Engagement with the auditory processing system during targeted auditory cognitive training mediates changes in cognitive outcomes in individuals with schizophrenia. *Neuropsychology* (2016).
5. Loewy R, ..., **Biagiante B, et al.** Intensive Auditory Cognitive Training Improves Verbal Memory in Adolescents and Young Adults at Clinical High Risk for Psychosis. *Schizophrenia Bulletin* (2016).
6. Schlosser D, ..., **Biagiante B, et al.** Modeling the role of negative symptoms in determining social functioning in individuals at clinical high risk of psychosis. *Schizophrenia Research* (2015).
7. Subramaniam K, ... , **Biagiante B, et al.** Neural signal during immediate reward anticipation in schizophrenia: Relationship to real-world motivation and function. *Neuroimage Clinical* (2015).
8. **Biagiante, B et al.** Dependency-like behaviors and pain coping styles in subjects with chronic migraine and medication overuse: results from a 1-year follow-up study. *BMC Neurology* (2014).
9. **Biagiante B** and Vinogradov S. Computerized Cognitive Training Targeting Brain Plasticity in Schizophrenia. In Michael M. Merzenich, Mor Nahum, Thomas M. van Vleet, editors: *Changing Brains - Applying Brain Plasticity to Advance and Recover Human Ability*, Vol 207, PBR, UK: Elsevier, (2013).
10. Gambini, O. , ..., **Biagiante B, et al.** Psychiatric screening for migraine patients. *Neurological Sciences* (2013).
11. Gambini, O. *et al.* Consultation-liaison psychiatry for patients with headaches. *Neurological Sciences* (2013).

Clinical and Translational Science Institute's (CTSI's) Strategic Opportunities Support (SOS): Digital Health Research - Improving Social Cognition in Patients with Severe Mental Illness: Neuroplasticity-Based Cognitive Training on a Mobile Device.

The goal was of this project was to evaluate the feasibility of delivering cognitive training and remote assessments using mobile devices.

Role: Postdoctoral Scholar.

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