The Effects of Atypical Antipsychotics and Schizotypy on Indexes of Semantic Processing

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Abstract

Electroencephalography (EEG) is an invaluable technique for measuring instantaneous brain activity during the performance of cognitive tasks. Using this method, event-related potentials (ERPs) can be obtained, where each ERP indexes a specific unconscious or conscious cognitive process depending on its time of onset, directionality and the stimulus that elicits it. The N400 is thus a negative ERP peaking at 400 ms and elicited by meaningful stimuli, such as words and is modulated by properties like semantic congruity and personality traits like schizotypy. The clinical importance of the N400 is apparent from the increasing amount of literature that demonstrates N400 anomalies in normal individuals with schizotypal tendencies and patients with schizophrenia. The hallucinations, delusions and disorganization that characterize schizophrenia are often dramatically reduced by antipsychotic medication. However, how antipsychotics produce their efficacy remains to be understood. Apart from their blockade of dopamine D2 receptors, little attention is given to understanding how they reduce the production of abnormal perceptions (hallucinations), how they restore the ability to dampen false beliefs in the presence of contradictory evidence, and how they limit the abnormal spreading of semantic activation that is thought to underlie disorganized thoughts and speech. According to some models of information processing, these effects could all be mediated by an increase of inhibitory processes brought about by these medications. To begin investigating this hypothesis, we tested the effect of a single minimal dose of the antipsychotic risperidone on ERPs elicited during two semantic tasks: a semantic categorization paradigm and a social role acceptance task in healthy individuals psychometrically identified as high or low schizotypes. Healthy participants were used to avoid confounds associated with using patient populations. Scalp electrical activity was measured before and 90 minutes after the beginning of the effect of 1 mg of risperidone (n=44) or a placebo (n=26) during the performance of the aforementioned tasks. Schizotypy was observed to modulate N400s elicited in the semantic categorization task and to be associated with accepting extraordinary social roles. While an increase in the frontal N400 amplitude was observed across all experimental groups in the semantic categorization task, the effect of risperidone was lateralized in both tasks. Additionally, risperidone was observed to increase the amplitude of the late positive component (LPC, 600-1000 ms). The implication of these results is discussed and potential explanations are proposed. While these results are

inconclusive on the effect of risperidone on the discussed ERPs, they point to another factor that has the potential to modulate the N400: session. We conclude that studies using the N400 as a marker of intervention efficacy should take precaution in employing similar paradigms.

Résumé

L'électroencéphalographie est une technique précieuse pour mesurer l'activité du cerveau en temps réel durant l'exécution de tâches cognitives. En utilisant cette méthode, les potentiels liés à l'événement, ou potentiels évoqués (PE) peuvent être calculés. Chaque PE indexe un processus cognitif conscient ou inconscient, selon le temps écoulé avant que le stimulus n'apparaisse, la polarité électrique du potentiel, ainsi que la tâche et le type du stimulus. Ainsi, le N400 est un PE de polarité négative qui culmine vers 400 ms. Son amplitude est modulée par diverses propriétés telles que la congruence sémantique du stimulus avec son contexte ou des traits de personnalité du sujet comme la schizotypie. L'importance clinique de la N400 est révélée par ses anomalies chez les individus normaux ayant une tendance schizotypique et chez les patients souffrant de schizophrénie. Les hallucinations, les délires et la désorganisation qui caractérisent cette affection sont souvent réduits par les médicaments antipsychotiques. Toutefois, les mécanismes par lesquels les antipsychotiques produisent ces effets restent incompris. Mis à part le fait qu'ils bloquent les récepteurs de dopamine D2, peu d'attention est consacrée à comprendre comment ils diminuent la production d'hallucinations, comment ils restaurent la capacité à atténuer les fausses croyances en présence de preuve contradictoire, et comment ils limitent la propagation anormale d'activité sémantiques qui serait à la base des pensées et des comportements désorganisés. Selon certains modèles de traitement d'information, tous ces effets pourraient dépendrent d'une augmentation des processus d'inhibition. Afin d'étudier cette hypothèse, nous avons testé les effets d'une seule dose minimale d'un antipsychotique, la risperidone, sur les PEs de deux tâches sémantiques: une catégorisation sémantique classique et une tâche d'acceptation de rôles sociaux. Les participants sains recrutés étaient catégorisés comme ayant des tendances schizotypiques basses ou élevées. Des participants réputés sains ont été utilisés pour ne pas que les effets de l'antipsychotique sur les PEs puissent être secondaires à une amélioration des symptômes cliniques de patients schizophrènes. L'activité électrique du cerveau a été mesurée avant (1ère session) et 90 minutes après (2ème session) le début de l'effet de 1 mg de risperidone (n=44) ou d'un placebo (n=26). La schizotypie a modulé les N400 de la tâche de catégorisation sémantique et de l'acceptance des rôles sociaux extraordinaires. Bien qu'une augmentation de la N400 ait aussi été observée dans le groupe placebo dans la tâche de catégorisation sémantique, celle-ci n'était pas latéralisée comme l'effet de la risperidone. De plus, la risperidone a augmenté

l’amplitude de la composante tardive positive (600-1000 ms). Les implications de ces résultats sont discutées et des explications possibles sont proposées. Alors que ces résultats sont peu concluants sur les effets du risperidone sur les PEs discutés, ils suggèrent qu’un facteur additionnel pourrait modifier l’amplitude de la N400 : la session. Nous concluons que les études qui utilisent la N400 comme un marqueur de l’efficacité des interventions doivent prendre des précautions lors de l’utilisation de paradigmes similaires.

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1. Introduction

1.1 *Schizotypy: a continuum from normality to schizophrenia*

Emerging research suggests that schizophrenia is not a categorical psychiatric disorder that is either present or absent in an individual (Claridge & Beech, 1995; Cochrane, Petch, & Pickering, 2012; Lenzenweger, 2006; Meehl, 1962; Nelson, Seal, Pantelis, & Phillips, 2013). Rather, dimensional models explaining the development of schizophrenia have been proposed. Of the most well-known theories is the *schizotypy model* theory, proposed by Meehl (1962, 1990). This theory posits that a latent personality organization along with a genetic liability is present within a subset of the general population, who go on to develop schizophrenia when sufficient environmental stressors are present. Recently, it has been argued that this model is insufficient to explain the heterogeneity of symptom presentation in schizophrenia (Nelson et al., 2013). Additionally, the model is criticized for falling short of explaining the mild psychotic experiences reported by at least 10% of the general population who do not develop schizophrenia (Verdoux & van Os, 2002). Alternatively, a fully dimensional model is proposed which suggests that schizotypy represents "natural central nervous system variations" that in their extreme manifest as the psychopathology of schizophrenia (Claridge & Beech, 1995; Nelson et al., 2013). Accordingly, all individuals in the general population fall on a schizotypy continuum that ranges from normality (i.e., low schizotypy) to schizophrenia (i.e., very high schizotypy accompanied with psychotic dysfunction).

Schizotypy then refers to a set of personality traits that are naturally variable, wherein extremes are categorized as schizophrenia. These personality traits correspond to those listed in the DSM-III-TR as criteria for schizotypal personality disorder and can be grouped in clusters that roughly correspond to the three major groups of schizophrenia symptoms. The cognitive-perceptual cluster includes magical thinking, delusional ideation and unusual perceptual experiences, and corresponds to the positive symptoms of schizophrenia. The interpersonal cluster describes social functioning abnormalities such as lack of close friends, social anhedonia and excessive social anxiety and parallels schizophrenia negative symptoms. Finally, the disorganized cluster refers to bizarre behavior and strange speech and corresponds to disorganization in schizophrenia (Nelson et al., 2013; Raine, 1991).

Various self-report measures have been developed to assess schizotypal personality traits in the non clinical population, such as the Perceptual Aberration Scale (PAS; Chapman et al., 1978), the Magical Ideation Scale (MIS; Eckblad & Chapman, 1983) and the Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE; Claridge et al., 1996). One of the most commonly used scales is the Schizotypal Personality Questionnaire (SPQ; Raine, 1991) whose 74 items are based specifically on the criteria for schizotypal personality disorder listed in the DSM-III-TR. Unlike the previously mentioned scales, the SPQ factor structure corresponds to the three groups of schizophrenia symptoms (i.e., positive, negative and disorganization) and thus provides a more accurate assessment of schizotypy. Further supporting the fully dimensional schizotypy continuum approach, it is observed that items on schizotypy scales are endorsed to a great degree by healthy non-clinical individuals (Johns & van Os, 2001). For instance, Verdoux et al. (1998) found that 1 in 10 individuals with no history of psychiatric illness report that they feel there is a conspiracy against them and 16% report having experienced verbal hallucinations (Verdoux & van Os, 2002).

Additionally, cognitive capacities appear to fall on the schizotypy continuum (Noguchi, Hori, & Kunugi, 2008). Individuals who score high on measures of schizotypy perform worse than low scorers on cognitive tasks in which schizophrenic patients exhibit pronounced deficits. Psychometrically identified schizotypes have been reported to perform worse on verbal IQ measures (Noguchi et al., 2008), to have deficits in visuospatial abilities (Daly, Afroz, & Walder, 2012), and to have overall worse executive function (Suhr & Spitznagel, 2001). Additionally, negative schizotypy of healthy individuals was found to predict reduced performance on a verbal fluency task while disorganization predicted reduced attention and cognitive inhibition in a negative priming paradigm (Cochrane et al., 2012). Consistent with the schizotypy continuum approach, schizophrenia patients were found to have stronger deficits in these tasks (Cochrane et al., 2012). Similarly, in a category fluency paradigm where participants are asked to generate as many exemplars as they could of a given semantic category in a limited amount of time, higher schizotypy scores were associated with more atypical exemplars than lower scores (Kiang & Kutas, 2006). Moreover, high schizotypes demonstrate a "jumping to conclusion" (JTC) bias, a key element implicated in the maintenance of delusions in schizophrenia patients (Sellen, Oaksford, & Gray, 2005). In addition, positive schizotypy, consisting of odd beliefs and magical thinking, is associated with reduced context maintenance (Fisher, Heller, & Miller, 2007). Taken

together, these findings provide support for the schizotypy continuum approach and point to a common domain in which shared cognitive deficits are present: semantic memory functioning.

1.2 *Semantic processing deficits and schizotypy*

Semantic memory refers to a memory construct that organizes knowledge about the world, facilitates understanding, and holds memories about meanings of words and concepts, as well as associations between different types of knowledge (Tulving, 1972). A prominent theory put forward to explain the organization of semantic memory posits that knowledge is organized in the form of highly interconnected networks where each concept is a node in a network and associations between concepts represent connections between these nodes (Collins & Loftus, 1975). The *spreading-activation model* of information processing suggests that the activation of one concept leads to a spread of activations of related concepts, where the greater the relatedness, the closer the proximity of the concepts in the network. In this model, the spread of activations to related concepts is viewed as automatic and immediate process, whereas the use of context for cognitive inhibition or generation of expectancy is viewed as an effortful and controlled process that requires attentional resources. The spreading-activation model is particularly used to explain the notion of *semantic priming*, where the processing of stimulus is facilitated when preceded by a semantically related context than when it appears alone or after a semantically unrelated context. For example, the processing of the word "table" is facilitated when it is preceded by the semantically related word "chair" than when its presented on its own or when it is preceded by the semantically unrelated word "sheep", as indicated by reaction time data. Following this framework, the onset of the word "chair" automatically activates representations of itself as well as semantically related concepts, like "table" in this example. Upon the presentation of the related target "table" less activation is then required and processing is facilitated. Generation of expectancy is thought to be driven by task dependent parameters and is thus considered a controlled process (Collins & Loftus, 1975; Kiang, 2010; Minzenberg, Ober, & Vinogradov, 2002).

Experimentally, semantic priming is assessed both behaviorally through analyzing reaction times to lexical decision or semantic categorization tasks and electrophysiologically through analyzing electrical brain activity elicited in such tasks. An *indirect* semantic priming

effect is taken to be the difference in reaction time between the unrelated target and the indirectly related target while a direct semantic priming effect is the reaction time difference between indirectly related and the directly related target. Together, these measures are used to assess automatic spread of activations within semantic memory networks.

Consistent with Eugene Bleuler's idea that schizophrenia is characterized by disorganization of knowledge in semantic memory networks (Bleuler, 1911), semantic priming abnormalities have been observed both in schizophrenia (Minzenberg et al., 2002) and schizotypy (Kiang, 2010; Morgan, Bedford, & Rossell, 2006). While it is difficult to generalize semantic priming deficits in schizophrenia patients due to confounds such as disease chronicity, medication use and heterogeneity of symptom presentation in this population, the literature indicates that abnormalities are reliably present in controlled as opposed to automatic semantic processing (Minzenberg et al., 2002). Experimentally, the use of either strategy is manipulated by adjusting the stimulus onset asynchrony (SOA) or the duration between the onset of the prime and the onset of the target word. In specific, an exaggerated spread of semantic activations in short SOA conditions (i.e., the automatic process) is observed where thought-disorder is the dominant symptom of the pathology (Kreher, Holcomb, Goff, & Kuperberg, 2008; Moritz, Woodward, Küppers, Lausen, & Schickel, 2003; Pomarol-Clotet, Oh, Laws, & McKenna, 2008; Spitzer, 1997). However, deficits in the controlled process (i.e. in long SOA conditions), marked by inefficient context use, are more homogeneously observed (Minzenberg et al., 2002). Together, these findings provide an explanation for the cognitive impairments and language deficits that accompany schizophrenia.

While semantic priming abnormalities are also observed in high schizotypal but healthy individuals, they are more subtle than in schizophrenia patients. In one study, highly schizotypal women were observed to judge indirectly related semantic associations as related compared to a low schizotypal control group at short SOAs, suggesting increased spread of activations within semantic networks in this population (Pizzagalli, Lehmann, & Brugger, 2001). It is important to note that in this study, only positive schizotypy was assessed (i.e., magical ideation and paranormal beliefs) rather than all clusters that underlie schizotypy. In another behavioral study, high schizotypes assessed on the Magical Ideation Scale were found to judge semantically unrelated words as more associated, further supporting the idea of enhanced spread of semantic

activations that would underlie paranormal ideation in this population (Mohr, Graves, Gianotti, Pizzagalli, & Brugger, 2001). Morgan et al. (2006) investigated the effect of schizotypy on semantic priming at short vs. long SOAs (automatic vs. controlled semantic priming), and on access to semantic memory through manipulating word frequency. High schizotypes were observed to have smaller semantic priming effects in the short SOA condition than in the long SOA condition, while low schizotypes displayed an opposite pattern. The authors suggest that reduced priming effects at short SOAs in the high schizotypy indicates *slower* spread of semantic activations whereas enhanced priming effects at long SOAs suggest more efficient context use to derive closer expectancies that compensate for impaired automatic processes (Morgan et al., 2006). Schizotypy did not affect semantic priming with respect to word frequency, suggesting that access and storage in semantic memory, like in schizophrenia, is not compromised in schizotypy (Doughty, Done, Lawrence, Al-Mousawi, & Ashaye, 2008). In general, this study concludes that automatic semantic priming is intact when global schizotypy is assessed, while controlled semantic priming deficits are associated with greater positive schizotypy.

Abnormalities in semantic processing appear to be a candidate feature of the deficits seen in schizotypy, and can be thought to underlie the tendency for delusional thinking on one end of the schizotypy continuum and full blown delusions and hallucinations at the other end. Additionally, patterns of activations within semantic memory networks provide an explanation for odd communication of schizotypy and idiosyncratic speech associated with schizophrenia.

1.3 *The electrophysiological study of semantic processing*

The controversial findings with respect to semantic priming in both the healthy and psychopathological expression of schizotypy are often explained by methodological differences across studies and subjective interpretations of behavioral data. However, electrophysiological evidence has emerged, in the past 50 years, providing a measure of brain activity during semantic processing. Electroencephalography (EEG) is a non-invasive imaging technique with a millisecond temporal resolution used to record electrical brain activity, both at rest and during the performance of cognitive tasks. Using this technique, brain activity elicited in cognitive tasks and time-locked to a stimulus onset is processed to construct what is known as event-related potentials (ERPs). Each ERP is characterized by the direction of its deflection (either negative or

positive), its scalp location, and how long after the stimulus onset it appears and reaches its maximum. Various ERPs have been identified, and each is thought to reflect a stage of cognitive processing, depending on the task and the type of stimulus that elicits it. With respect to semantic processing, the negatively peaking ERP maximal at approximately 400 ms after the onset of potentially meaningful stimuli at centro-parietal scalp sites has been intensively investigated. This ERP, termed the N400 ("N" to signify its negativity and 400 to signify its peak time), was first identified by Kutas & Hillyard (1980) where it was found to occur in response to sentence endings that were incongruent to the sentence frame (e.g., "I shaved my moustache and *eyebrows*" compared to "I shaved my moustache and *beard*"). Since then, it has been established that the N400 is elicited by any potentially meaningful stimuli, including faces, objects, and sounds (Kutas & Federmeier, 2011).

The implication of this ERP in the early stages of cognitive processing, namely in semantic processing, comes from studies investigating which factors modulate its amplitude. Semantic incongruity is the most well-established modulator of the N400 amplitude, where it is observed to increase the N400 amplitude (see Kutas & Federmeier, 2011 for a review). Non-semantic factors are also influence the amplitude of this ERP, for example frequency and repetition. In essence, frequent and highly repeated stimuli elicit smaller N400s (Kutas & Federmeier, 2000). Fundamentally, factors that facilitate processing are observed to reduce N400 amplitude while those that increase processing difficulty increase its amplitude (Kutas & Federmeier, 2009). This can be explained by the semantic priming process previously described, where smaller N400 amplitudes are associated with greater semantic priming effects. While consensus on the exact functional significance of this ERP is yet to be established, theories have been put forward that implicate it in processes related to semantic integration (Kutas & Hillyard, 1980) , semantic inhibition (Debruille, 2007), or retrieval from semantic memory (Laszlo & Federmeier, 2010).

There is a wealth of literature investigating the N400 as an index of semantic processing in schizophrenia, in an effort to shed light on the deficits present in this population. Smaller amplitudes and diminished N400 effects (i.e., the difference in amplitude of N400s elicited by unrelated and directly related targets) have been reported in short SOA paradigms (Kostova & Passerieux, 2003; Kostova, Passerieux, Laurent, & Hardy-Baylé, 2005; Niznikiewicz, Mittal, Nestor, & McCarley, 2010), while larger N400 amplitudes have been observed in long SOA

paradigms (Condray, Steinhauer, Cohen, van Kammen, & Kasparek, 1999; Kiang, Christensen, Kutas, & Zipursky, 2012). These findings together support an increased automatic spread of activation accompanied by deficits in context use in schizophrenia (Mohammad & DeLisi, 2013). In accordance with the schizotypy continuum approach, abnormalities in the N400 amplitude have also been reported in high compared to low schizotypy healthy individuals (Kiang & Kutas, 2005; Prévost, Rodier, & Renoult, 2010). In one study, SPQ scores were found to correlate with larger N400s for both strong and weak associates of a given category, and with smaller N400s for non-exemplars at long SOAs suggesting poor context use in schizotypy (Kiang & Kutas, 2005). Another study reported a smaller N400 effect with increasing degrees of schizotypy (Kimble, Lyons, & O'Donnell, 2000). Kiang et al. (2010) reported smaller N400 indirect priming effects with increasing SPQ scores at both short and long SOAs, indicative of hyper-activations in semantic networks as well as inefficient context use. Moreover, individual schizotypy clusters are observed to correlate differentially with the N400. For instance, Prevost et al. (2010) found that N400 amplitudes elicited by unrelated and related targets were larger in high schizotypy individuals, and that these amplitude correlated with scores on the disorganization and interpersonal clusters of the SPQ. Kiang et al. (2010) found that smaller N400 effects correlated with scores on the cognitive-perceptual cluster of the SPQ, implicating semantic processing deficits in the maintenance of abnormal beliefs.

Another ERP component implicated in semantic processing is the late positive component (LPC) appearing around 600 ms after stimulus onset (Juottonen, Revonsuo, & Lang, 1996). While the process reflected by this positively-going ERP is less clear than that of the N400, it has been observed in semantic tasks that require memorization (Bentin & McCarthy, 1994; Curran, Tucker, Kutas, & Posner, 1993; McCallum, Farmer, & Pocock, 1984) or making truth-value decisions on congruency (Holcomb & Neville, 1991). Due to its late onset (i.e. around 600 ms post-stimulus), it has thus been suggested that this ERP occurs after complete stimulus processing and perhaps indicates conscious evaluative processes (Juottonen et al., 1996) or recollection processes. Fundamentally, the LPC is thought to reflect "the extended retrieval of semantic and episodic information and the integration of that information with the contents of working memory" (Petten, Kutas, Kluender, Mitchiner, & McIsaac, 1991), while the N400 reflects implicit memory processes (Olichney, Petten, & Paller, 2000). In schizophrenia, reduced LPC amplitudes are observed and this is taken to suggest impairments in integrating activated

information with current contexts (Andrews et al., 1993; Brecher, Porjesz, & Begleiter, 1987). Whether LPC deficits exist in schizotypy is yet to be established, but Ward et al. (1986) reported similar reductions in the amplitude of this ERP.

Event-related potentials provide an invaluable tool for the measurement of instantaneous brain activity during the performance of cognitive tasks. While the N400 gives insight into unconscious brain processes, the LPC can shed light on conscious recollection processes and together they can be used to elucidate information about cognitive impairments that underlie the symptomology of schizophrenia. Moreover, experimental manipulations of task parameters, study design, and characteristics of subject sample can lead to a further understanding of schizotypy, both in its normal and psychopathological forms.

1.4 *The neurobiology of semantic processing: the role of dopamine*

A landmark study conducted by Brozoski et al. in 1979 revealed that catecholamine depletion in the prefrontal cortex of rhesus monkeys produced severe cognitive deficits, comparable to deficits seen when this part of the cortex is removed (Brozoski, Brown, Rosvold, & Goldman, 1979). Since then, the role of the catecholamine dopamine in regulating cortical and subcortical networks involved in cognitive functioning has been well established (Cohen & Servan-Schreiber, 1992; Copland, McMahon, Silburn, & de Zubicaray, 2009). With respect to semantic memory and processing, it is theorized that dopamine acts as a neuromodulator where it amplifies strong activations within semantic networks and dampens weak activations (Kischka et al., 1996; Servan-Schreiber, Printz, & Cohen, 1990). Fundamentally, dopamine acts to focus relevant semantic activations closely associated with a presented stimulus and silencing activations that are distant or weakly associated with the presented stimulus. This effect has been described as the signal-to-noise ratio (SNR), and greater dopamine activity is described to increase the SNR, while lower activity decreases it (Copland et al., 2009). Consistent with this, the administration of L-dopa to healthy individuals, mimicking schizophrenic brains, produced reduced indirect semantic priming but only marginally affected direct semantic priming (Kischka et al., 1996).

The involvement of dopamine in the symptomology of schizophrenia has been heavily investigated since the incidental discovery of the therapeutic effects of dopamine antagonists on this psychopathology. While the exact mechanisms underlying the disorder are unknown, neurobiological research has revealed abnormalities in the neurotransmitter dopamine (DA). Current theories, supported by findings from various imaging studies, posit that a reduction of dopaminergic activity in the frontal lobes accounts for the negative symptoms and cognitive deficits while increased dopaminergic activity in subcortical areas is responsible for positive symptoms (Howes & Kapur, 2009; Stone, Morrison, & Pilowsky, 2007). In line with the schizotypy continuum, subtle but similar structural and neurobiological abnormalities to those seen in schizophrenia have also been observed in healthy but highly schizotypal individuals (Corlett & Fletcher, 2012; Siever & Davis, 2004; Tsuang, Stone, Tarbox, & Faraone, 2002). The above-described functions of dopamine in semantic processing could then account for the semantic processing deficits seen along the schizotypy continuum.

Mohr et al. (2005) found that schizotypy modulated hemispherical dominance in language processing. Schizotypy was observed to be associated with dominant right hemisphere contribution in lexical processing and the administration of L-dopa restored left-hemisphere contribution, by decreasing right hemisphere dominance in positive schizotypy but by increasing left hemisphere dominance in negative schizotypy (Mohr et al., 2005). These findings speak to the subtlety of language processing abnormalities in healthy but highly schizotypal individuals, and describe compensatory mechanisms that prevent the transition of healthy schizotypy into a pathological state.

Given the role of dopamine in modulating semantic networks and semantic processing deficits seen in schizophrenia patients, the extent to which antipsychotics affect semantic networks becomes an important area of study. In a 2011 meta-analysis of the N400 as an index of semantic processing in schizophrenia patients, Wang et al. report that while many studies fail to show a significant effect of antipsychotics on the N400, antipsychotic dosage moderates the effect size of the N400 effect and raw N400s of congruent/related conditions (Wang, Cheung, Gong, & Chan, 2011). In particular, the authors suggest that this relationship might be mediated by illness severity and baseline dopaminergic transmission in schizophrenic brains. In a study controlling symptom severity in schizophrenic patients, Condray et al. compared N400s of

patients receiving haloperidol maintenance therapy versus placebo replacement (Condray et al., 1999). Compared to healthy controls, an absence of the semantic priming effect was observed in patients in the placebo group and haloperidol weakly, although insignificantly, restored this effect. Considering the confounds of previous antipsychotic use in patient groups, previous work in our lab investigated scalp activity during the performance of a semantic categorization task after taking a single minimal dose of olanzapine in healthy drug-naive participants (Debruille, Rodier, Prévost, Lionnet, & Molavi, 2013). Relative to a placebo, olanzapine decreased *frontal* N400 amplitudes elicited in a semantic categorization task, approximately 15 hours after its administration in the high, but not low, schizotypy group. Furthermore, olanzapine was observed to have no influence on ERPs elicited by meaningless stimuli, in an auditory oddball task. These results point to the specific effect of antipsychotics on semantic memory networks, consistent with the involvement of dopamine in modulating them. In particular, olanzapine was suggested to limit the spread of semantic activations elicited by target words and/or reduce required inhibitory processes. The greater impact on *frontal* N400s is thought to reflect modulation of action representations associated with concrete words that involve prefrontal networks. In order to further explore this effect on frontal N400s, the next step would be to use semantic stimuli that specifically activate action representations and observe the ERPs they elicit and their modulation by antipsychotics. As such, we developed a bank of social role stimuli that were observed to elicit the N400 ERP in pilot studies (Fernandez Cruz et al., 2013).

1.5 *The semantic nature of social roles*

From a semantic perspective, social roles are described as the mode of participation of an entity in an event (Hornstein, 1993; Masolo, Vieu, Bottazzi, & Catenacci, 2004). Following the spread-activation model of information processing, social roles are viewed as "concepts within a mental space that can have values within another mental space by means of a counterpart relation" (Fauconnier, 1988; Masolo et al., 2004). Like names of animals and objects, social role stimuli can be classified as semantic stimuli and their presentation would elicit a spread of activation of related roles, associated behaviors, and personality traits within semantic memory. In a review of the relevant N400 literature, Polich states that N400-like potentials appear whenever semantic representations of a word are accessed over a wide range of experimental

paradigms and also whenever some type of stimulus matching is required (Polich, 1985). Additionally, self-referential judgements have been documented to elicit negativities at 400 ms (Polich, 1985). In particular, behavioral data points to another type of semantic priming effects with respect to the self, where it is reported that semantic processing is facilitated when judgements relate to the self than when they relate to the other (Watson, Dritschel, Obonsawin, & Jentzsch, 2007). For instance, reaction times are significantly shorter in judgements of personality traits with respect to the self than with respect to another (e.g., "*I am* friendly" vs. "*My best friend* is intelligent"). This is further accompanied by smaller fronto-central N400s to self than non-self judgements (Watson et al., 2007). Furthermore, fMRI data implicates the prefrontal cortex in the processing of self judgements compared to non-self judgements, explaining the modulation of *fronto-central* N400s by such parameters (Kelley et al., 2002). As such, the novel task reported here presents social roles within a self fit framework, where participants are asked to decide whether or not they can consider themselves playing a presented social role, in order to elicit frontal N400s. This would allow for an examination of why antipsychotics specifically impact the frontal N400.

The importance of studying the semantic processing of social roles in relation to schizotypy is apparent given the range of social dysfunction seen along the schizotypy continuum. Emerging research has attributed this dysfunction to deficits in empathy (Henry et al., 2009; Henry, Bailey, & Rendell, 2008), interpersonal sensitivity (Miller & Lenzenweger, 2012) and emotion recognition (Brown & Cohen, 2010) in psychometrically identified schizotypes. However, social behavior within a societal framework is yet to be investigated in this population. This type of social behavior is thought to be driven by perceptions of the self-concept, a collection of beliefs about oneself. Self-concept differentiation refers to the tendency to see oneself as having different personality characteristics across different social roles and has been associated with poor psychological adjustment in healthy individuals (Donahue, Robins, Roberts, & John, 1993). The present social role acceptance paradigm is designed to investigate the fit of different categories of roles with the self-concept as a function of schizotypy. In specific, roles in this bank of stimuli are categorized according to their ordinariness and advantageousness. Determining the degree to which roles from each category are accepted or rejected according to schizotypy will allow for an understanding of social role appraisal in this population. Furthermore, given the tendency for delusional ideation seen in this population,

determining whether schizotypy is related to the ordinariness and/or advantageousness of roles endorsed would provide another measure of their tendency for delusional thinking. ERP measures will further enable us to investigate brain activity involved in making real-life decisions: accepting or rejecting a social role.

1.6 *Research objectives*

Taken together, emerging research provides an explanation for the therapeutic effects of antipsychotics in schizophrenia, where they reduce hallucinations, dampen delusional thinking, and seem to restore cognitive functioning in patients (Cuesta, Peralta, & Zarzuela, 2001; Harvey & Keefe, 2001; Sharma & Mockler, 1998). The aims of the present project are thus two-fold. First, we investigate the effect of schizotypy on brain potentials elicited in semantic tasks. Second, we examine the immediate effect of the atypical antipsychotic risperidone on these brain potentials to elucidate a possible effect on semantic processing. Risperidone is used here to determine whether the previously observed effect of olanzapine is due to the antipsychotic properties of the medication. The effect of risperidone is investigated on ERPs elicited by two tasks: a semantic categorization paradigm well-established to elicit the N400 ERP and a novel social role acceptance task designed to assess ecologically valid choices pertinent to the social sphere. Consistent with the role of dopamine in semantic processing, we hypothesize that the immediate effect of antipsychotics will be an augmentation of the frontal N400 amplitude, reflecting decreased focusing of activations and thus reduced use of context in the semantic categorization paradigm. For the social roles paradigm we expect to see greater acceptance of extraordinary roles by individuals scoring high on the SPQ. We expect to see a similar effect of risperidone on the N400 as that expected in the semantic categorization paradigm, following the semantic nature of social role stimuli. Given the self-referential judgments required in this task, we also hypothesize to see modulations of the LPC amplitude, reflecting an effect on the evaluative processes elicited by this task

The present study aims to determine the effect of antipsychotic medications on indexes of semantic processing as a measure of their long term outcome in patients. As it is not possible to perform a placebo-controlled crossover design in patient populations, we employ a between-group design in the current protocol. Consistent with the goal of adapting a one day test for

patients, a duration of 90 minutes was allowed for the observation of an electrophysiological effect of risperidone. Pharmacologically, risperidone has a half-life of 3 hours and 90 minutes is deemed enough to begin observing an effect in the brain.

Results from the investigation of ERP differences during semantic processing between high and low schizotypy individuals will further contribute to the literature on the schizotypy continuum approach. Additionally, few studies have attempted to investigate the effect of the common schizophrenia treatment, antipsychotics, on semantic processing and this study will further knowledge in this area. Finally, understanding whether antipsychotics have a bearing on semantic processing would provide insight to the degree of which testing schizophrenia patients under medication can influence research outcomes.

2. *Methods*

2.1 *Participants*

Eighty-one right-handed participants (39 females) between 18 and 30 years old (mean age: 23.3), having normal or corrected to normal vision were recruited through English and French online advertisements. Participants were either native English or French speakers or had completed a minimum of 10 years of education in either language (mean= 14.6 years). Exclusion criteria included current or past DSM-IV Axis I disorders- except for depressive episodes that were resolved at least two years ago-, alcohol and drug abuse, neurological or medical conditions that compromise brain functioning, and history of head injury with loss of consciousness longer than 5 minutes. Participants were in one of four experimental groups based on treatment and schizotypy: risperidone medicated and high schizotypy, risperidone medicated and low schizotypy, placebo and high schizotypy, and placebo and low schizotypy.

2.2 *Experimental procedure*

Figure 1 outlines the experimental procedure on the testing day. Participants were invited to the lab for one 4-hour testing session. Upon arrival, the experimental procedure was explained as previously agreed with the Research and Ethics Board of the Douglas Mental Health

University Institute and signed informed consent was then obtained. Next, participants completed a battery of questionnaires (described below) administered in their preferred language (English or French) and the electrode cap was placed. After being briefly described the semantic categorization and social role acceptance tasks, participants were seated comfortably in a dimly lit room 1 m from a computer screen. The tasks were always performed in that order, and the first session of each was preceded by a short practice run. Instructions and stimuli were, like the questionnaires, given in the participants' preferred language. After the practice run of the semantic categorization task, 1 mg of the orally disintegrating Risperdal M-Tab© tablet, or an orally disintegrating placebo was administered. For both, the emptiness of the mouth was checked after chewing and swallowing. Immediately after, the first session of EEG recording began while the participant performed the first sequence of the semantic categorization task (session 1), followed by the social role acceptance task. Participants were then given a one-hour lunch break. The second EEG recording session thus began 90 minutes after the administration of risperidone or placebo (session 2). This short time window was chosen to allow for the investigation of the immediate effects of risperidone. A neurochemical effect of this dose was assumed to occur at after this delay in accordance with the medication's peak plasma concentration of 1 hour (U.S. Food and Drug Administration, 2012). In session 2, participants performed the second sequence of the semantic categorization task followed by the second sequence of the social role acceptance task. Finally, in the debriefing session participants provided feedback about the experiment and completed the two post-experiment questionnaires (described below).

Figure 1. Sequence of events on the testing day

2.3 *Questionnaires*

Participants were asked to give their age, gender and number of years of education. They were also asked to confirm that they were right-handed and had perfect or corrected-to-normal vision. Participants reported whether they were smoking or not and were asked about their alcohol and recreational drug use habits. Participants who did not meet inclusion criteria (see below) were excluded. Both at the beginning and end of the testing session participants were asked to rate, on a scale of 1 to 10, their levels of energy, sleepiness, thought crowdedness, thought sharpness, distraction, current mood and mood intensity. In addition, at the end of the session participants were asked to rate the degree to which they felt the following symptoms, if at all: headache, abdominal pain, muscle stiffness, dry mouth, increased appetite, and agitation.

Current anxiety state was assessed using the state anxiety questions of the STAI (Spielberger et al., 1983; Bruchon-Schweitzer & Paulhan, 1993 for French translation). On a 4-point scale participants rated the frequency of nervousness and discomfort, among other things, experienced at the beginning and end of the testing session. This questionnaire was used to control for any reductions in anxiety possibly brought about by the antipsychotic dose.

The presence of schizotypal personality traits was assessed using the schizotypal personality questionnaire (SPQ; Raine, 1991; Dumas et al., 1998 for French translation), which is based on the DSM III-TR criteria for schizotypal personality disorder. The 74 items in this questionnaire fall into 9 subscales that can further be grouped into 3 clusters. The cognitive-perceptual cluster includes the 'Ideas of Reference' and 'Odd Beliefs or Magical Thinking' subscales. The interpersonal cluster includes the 'Excessive Social Anxiety', 'No Close Friends', 'Constricted Affect' and 'Suspiciousness' subscales. Finally, the disorganization cluster consisted of the 'Odd Speech' and 'Odd or Eccentric Behavior' subscales. For each of these clusters, a score is computed by adding the scores for each of its subscales.

Delusional ideation was assessed using the Peters' et al. Delusional Inventory (the PDI; Peters et al., 1999; Peters & Garetty, 1996 for French version). In addition to a global score reflecting the presence of delusional ideas, it provides measures of the conviction, distress and preoccupation accompanying these delusions. This questionnaire was used alongside the SPQ since its questions are presented in a form more likely to be endorsed by the general populations for which it has been designed (e.g., "Do you ever feel/think..as if..").

2.4: *Tasks*

2.4.1: Semantic Categorization

A semantic categorization paradigm well known to elicit the N400 ERP was used in this experiment (Debruille et al., 2010). Figure 2 describes the experimental sequence of this task. In each of the two sessions, a total of 180 trials were presented to subjects. Each trial included the serial presentation of two black words presented against a white background. In two-thirds (i. e., 120) of the trials, the first of these two words was the prime 'ANIMAL'. It was followed by a target word that matched the prime category (i.e., an animal name; e.g., dog) in 50% (i. e., in 60) of the trials or one that did not match the prime category (i.e., an object name; e.g., couch). Participants were instructed to respond as fast and as accurately as possible by pressing a 'YES' button in the match condition and 'NO' in the mismatch condition. In the 60 remaining trials, the word 'INACTION' was presented as a prime. It was also followed by a matching or a mismatching target with equal probabilities of occurrence. However, in these trials, participants

were instructed not make a response. The purpose of this 'INACTION' condition was to prevent habituation to the 'ANIMAL' prime. 'ANIMAL' AND 'INACTION' trials were mixed at random. These two primes were shown for 500 ms and immediately replaced by a fixation cross that lasted 500 ms, after which the target was shown for 1 second. Participants could make their response while the target was on screen and were given an additional 500 ms after the target disappeared. The word 'BLINK' appeared 1.5 to 2 ms after the target onset, during the presentation of which the participants could blink without disrupting the electroencephalogram (EEG) of the trial. The stimulus onset asynchrony (SOA) in this experiment was thus 1 second. The mean number of letters of the animal and object target words were matched as well as their mean frequency of usage, using the Content *et al.*, (1990) data base for the French words and the Kucera & Francis (1967) counts for the English words. Target words were only presented once. There was no repetition across the first and second session of testing and the particular stimulus sequences used for the sessions were counterbalanced across participants in both medication and placebo groups.

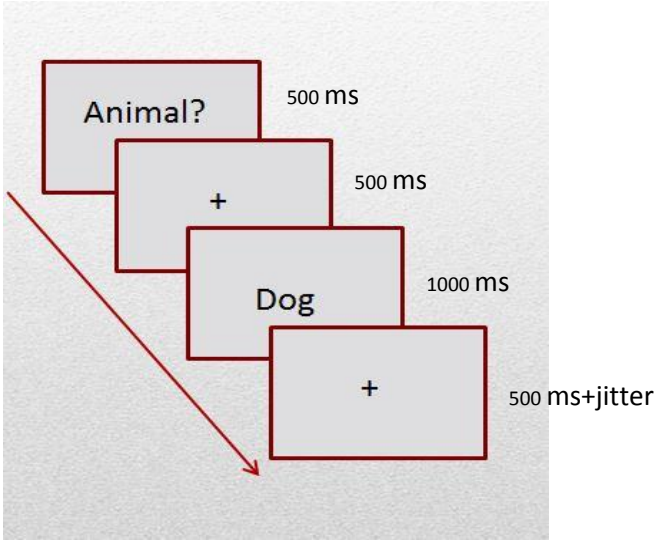

Figure 2. Semantic Categorization task experimental sequence

2.4.2 Social Role Acceptance

In addition to the semantic categorization task, a novel and more ecologically valid social role acceptance paradigm was used. Here, participants were presented with names of social roles one by one and were asked to consider whether they could consider themselves playing the presented role at any moment in their life (i.e. accept the role) or not (i.e. reject the role). The experimental sequence of this task is presented in figure 3. In each session 200 roles were presented and the sequences were counterbalanced across sessions. Roles were divided into 4 groups based on their ordinariness and advantageousness, as characterized by independent raters in a previous study. Ordinariness referred to whether or not the role was out of the usual or regular course of order, exceeded human capability and could be performed by average persons. Advantageousness referred to whether or not the role benefited the individual playing it. As such, a role could be ordinary advantageous (e.g., parent), ordinary disadvantageous (e.g., blind person), extraordinary advantageous (e.g., God) or extraordinary disadvantageous (e.g., executioner). Each role was presented for 500 ms and was followed immediately by a fixation cross that lasted for 500 ms. The word 'BLINK' appeared after every 5 social roles and lasted for a duration of 500 ms. Participants were asked to make 'YES' or 'NO' responses using the same response pad used in the semantic categorization task. The mean number of letters and frequency of the role was controlled for across categories. Participants were unaware of the role categories.

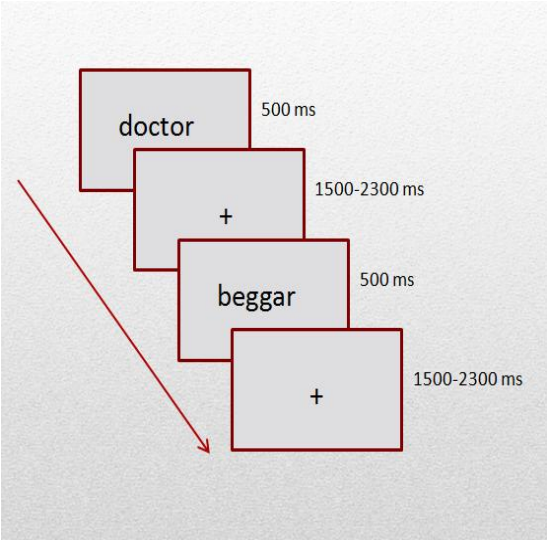

Figure 3. Social role acceptance task experimental sequence

2.5 *Data acquisition and processing*

Accuracies and response times were recorded for each action trial and the EEG was captured using electrodes from the ECI cap (Electro-cap International) placed according to the modified expanded 10-20 system (Electron position Nomenclature, 1991), with linked ears used as a reference. The 28 electrodes used were grouped into a sagittal subset comprising Fz, Fcz, Cz and Pz; a parasagittal subset including Fp1/2, F3/4, Fc3/4, C3/4, Cp3/4, P3/4 and O1/2; and lateral subset encompassing F7/8, Ft7/8, T3/4, Tp7/8 and T5/6. The impedance, which was measured before the beginning of the experiment using a 30Hz current, was kept below 5 kOhms. The half amplitude cut-offs of high- and low-pass frequency filters were set at 0.05 and 50 Hz, respectively. EEG signals were digitized at a 256 Hz sampling frequency and stored along with the stimulus and response codes.

In the semantic categorization task, trials having incorrect responses or response times shorter than 200 ms or longer than 2000 ms were rejected. Baseline correction was set between -200 and 0, pre-stimulus onset. Trials with amplitudes greater than or lesser than 100 μv were rejected. This included those with excessive eye movements. On average, 20% of trials were rejected. Averages for action trials were calculated over the time period of 200 ms pre target onset up to 1200 ms later. Trials corresponding to the 'INACTION' target words were not analyzed. The time window 300-500 ms was used to analyze the N400.

In the social roles acceptance task, the same data processing criteria as the semantic categorization task applied, except for a few differences. Here, trials with response times shorter than 300 ms were rejected. Additionally, the time window used to analyze the N400 was set to 250-550 ms. Because of the nature of the stimuli used, the late positive component (LPC) ERP was also analyzed, here in the 600-1000 ms time window. Participants were retained in this analysis only if a minimum of 50 trials survived rejection criteria.

2.6 *Statistical Analyses*

2.6.1 Semantic categorization task

A median split of SPQ scores divided participants into high and low schizotypy groups in the risperidone and placebo groups. Percentage of accurate responses and mean reaction times were analyzed for target words of the "ANIMAL" prime trials only. Mixed-model repeated measures ANOVAs were done separately for accuracies and reaction times, with session (session 1 vs. session 2) and condition (match vs. mismatch) as within-subject factors. Treatment group (medication vs. placebo) and schizotypy (high vs. low) were entered as between-subject factors.

For the N400, three mixed-model repeated measures ANOVAs were performed, one for each electrode subset. As with the behavioral data, session and condition were entered as within-subject factors. Treatment group and schizotypy were entered as between-subject factors. Electrode was added as a third within-subject factor. Hemiscalp (left vs. right) was added as a fourth within-subject factor for the parasagittal and lateral electrode subsets. Additional analyses were done to find the source of the interactions found. We used the Greenhouse and Geisser (1959) procedure to compensate for heterogeneous variances for the factor having more than two levels, that is, for electrode site. In each case, the original degrees of freedom are reported together with the *Epsilon* (E) correction factor and the corrected probability level.

2.6.2 Social roles acceptance task

Percentage of accepted responses in each of the 4 categories and reaction times corresponding to acceptance/rejection, ordinariness, and advantageousness were analyzed. Mixed-model repeated measures ANOVA was done separately for percentage of accepted roles and reaction time. For role acceptance, session (session 1 vs. session 2), ordinariness (ordinary vs. extraordinary), and advantageousness (advantageous vs. disadvantageous) were entered as within-subject factors; treatment group (medication vs. placebo) and schizotypy (high vs. low) were entered as between-subject factors. The same factors were used in analyzing reaction times, with the addition of decision (accepted vs. rejected) as a within-subject factor. As percentages of

accepted roles were analyzed rather than raw numbers, it was not necessary to include decision as a within subject factor in that analysis.

For the N400 and the LPC, three mixed-model repeated measures ANOVAs were performed, one for each electrode subset. Session, decision, and electrode were entered as within-subject factors; treatment group and schizotypy were entered as between-subject factors. ERPs were not analyzed by category as an insufficient number (<20) of roles in certain categories survived rejection during analysis. Hemiscalp (left vs. right) was further added as a within-subject factor for the parasagittal and lateral electrode subset ANOVAs. Additional analyses were done to find the source of the interactions found. We used the Greenhouse and Geisser (1959) procedure to compensate for heterogeneous variances for the factor having more than two levels, that is, for electrode site. In each case, the original degrees of freedom are reported together with the *Epsilon* (E) correction factor and the corrected probability level.

3. *Results*

3.1. Experiment 1: Semantic Categorization task

Participants with inaccuracy greater than 20% and reaction times shorter than 200 ms or longer than 2000 ms, were excluded from this analysis. A total number of 70 participants thus remained: Risperidone medicated and high SPQ score = 22; Risperidone medicated and low SPQ score = 22; Placebo and high SPQ score = 14; placebo and low SPQ score = 12).

3.1.1. *Questionnaire measures*

Table 1 shows the demographic and clinical characteristics of the participants with high compared to low schizotypy and those taking risperidone compared to those taking placebo. A t-test revealed no significant differences between the risperidone and placebo groups in the mean global SPQ score (t(68)= -2.4; *p*=.862) or the mean total PDI score (t(66)= -2.5; *p*=.428). However, the mean global SPQ and PDI scores were significantly higher for the low scorers taking placebo than the low scorers taking risperidone (SPQ: t(32)= -3.9; *p*=.001, PDI: t(30)=-

5.1; $p<.001$). Furthermore, global SPQ and PDI scores significantly correlated for all participants (pearson r= .79; $p=<.001$). Repeated measures ANOVA on the STAI did not show a significant difference in anxiety state from the beginning to the end of the testing session, for either the medication or placebo groups ($F(1,62)= .133$; $p=.717$). Both the medication and placebo groups reported significantly: lower energy levels ($F(1,64)= 56.1$; $p<.001$), increased sleepiness ($F(1,64)= 16.7$; $p<.001$), more crowded thoughts ($F(1,64)= 6.9$; $p=.011$), decreased thought sharpness ($F(1,64)= 47.1$; $p<.001$), increased distraction ($F(1,64)= 6.0$; $p=.017$), lowered mood ($F(1,64)= 21.0$; $p<.001$), lower mood intensity ($F(1,64)= 7.0$; $p=.01$) and less influence of their thoughts on mood ($F(1,64)= 9.5$; $p=.003$) at the end of the testing session. Only participants in the risperidone medicated group reported significantly slower thought ($F(1,43)= 37.6$; $p<.001$) at the end compared to the beginning of the testing session. Scores on the energy levels and mood questionnaire did not differ with schizotypy. Independent sample t-test showed a significant difference between the placebo and medication group in the following reported side effects commonly associated with risperidone: dry mouth ($t(68)=1.9$; $p=.004$). Here, participants taking risperidone reported increased mouth dryness (mean rating = 2.8) compared to those taking placebo (mean rating = 1.9).

	Risperidone medicated group N= 44		Placebo group N=26	
	High SPQ N=22	Low SPQ N=22	High SPQ N=14	Low SPQ N=12
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)
Mean age	24.6 (3.3)	23.6 (2.8)	21.4 (2.6)	22.8 (2.5)
Numbers of years of study	14.6 (1.4)	14.6 (1.4)	14.6 (1.8)	14.6 (1.8)
Mean global SPQ scores	33.9 (10.0)	9.2 (6.0)	40.4 (12.0)	18.6 (7.8)
Mean scores for cognitive-perceptual cluster of SPQ	7.2 (3.3)	2.5 (2.9)	8.9 (2.7)	6.4 (3.5)
Mean scores for interpersonal cluster of SPQ	15.1 (7.6)	3.6 (3.7)	17.1 (8.0)	6.7 (5.9)
Mean scores for disorganization cluster of SPQ	8.8 (3.1)	2.4 (2.1)	9.9 (3.3)	3.9 (3.9)
Mean total PDI scores	8.4 (3.7)	2.2 (1.6)	9.6 (3.8)	6.3 (3.0)

Table 1. Demographic and clinical characteristics of the risperidone medicated and placebo groups included in the semantic categorization task.

3.1.2. ***Behavioral results***

Repeated measures ANOVA revealed a significant main effect of condition on percentage accuracy ($F(1,66)= 40.9$; $p<.001$) where participants were more accurate categorizing object names, i.e. mismatch condition, (96.6 %, +/- 2.7%) than animal names, i.e., match condition, (93.2 %, +/- 4.8%). A session x condition x treatment group 3-way interaction was

also observed for percentage accuracy (F(1,66)= 6.7; *p*=.012). Posthoc analysis revealed that accuracy increased for the match condition for participants in the risperidone group only (F(1,42)= 5.1; *p*=.029).

For reaction times, a main effect of condition was observed (F(1,65)= 81.3; *p*<.001). Here, participants were faster at categorizing animal names (698.7 ms, +/- 150.5 ms) than object names (758.9 ms, +/- 156.4 ms).

3.1.3. *ERP results*

A main effect of condition was observed at each electrode subset (sagittal (F(1,66)= 91.1; *p*<.001), parasagittal (F(1,66)= 97.5; *p*<.001) and lateral (F(1,66)= 78.6); *p*<.001). The amplitude of the N400 was larger in the mismatch than the match condition. At all electrode subsets, condition x electrode interactions were further observed (sagittal (F(3,198)= 18.8; *p*<.001; epsilon=.48) , parasagittal (F(6,396)= 22.1; *p*<.001; epsilon=.35), and lateral (F(4, 264)= 17.0; *p*<.001; epsilon=.39)). ERPs elicited in the mismatch condition were significantly larger than those elicited in the match condition at all electrodes (*p*s<.001), however the difference was maximal at centro-parietal electrodes. At sagittal electrodes, ANOVAs yielded a significant condition x schizotypy interaction (F(1,66)= 5.6; *p*=.021). Although the condition effect was significant for both high and low schizotypy groups, the difference in amplitude between the N400s of the match and mismatch conditions was larger for the low than high schizotypy group (Posthoc analyses revealed that here, the mismatch-match difference was larger for low schizotypy than high schizotypy groups (3.156 μv vs. 1.905 μv). A condition x electrodes x schizotypy interaction was observed at parasagittal (F(6,396)= 4.3; *p*=.015; epsilon=.35) and lateral (F(4,264)= 5.3; *p*=.012; epsilon=.39). For these electrode subsets, posthoc analyses revealed that the mismatch-match difference was larger for the low schizotypy group than the high schizotypy group, specifically at centro-parietal sites. At the parasagittal electrodes, a condition x electrodes x treatment group interaction was observed (F(6,396)= 3.5; *p*=.032; epsilon=.35) and posthocs showed that the centro-parietal mismatch-match difference was larger in the placebo than the risperidone medicated group.

Additionally, ANOVAs revealed a significant condition x electrodes x hemiscalp interaction at parasagittal electrodes ($F(6,396)= 3.0$; $p=.017$; epsilon=.73). Here, posthocs showed that the mismatch-match effect was maximal at the parietal electrodes over the right than left hemiscalp. Similarly, a condition x hemiscalp interaction in the lateral electrode subset ($F(1,66)= 7.9$; $p=.007$) revealed that the mismatch-match difference was larger over the right than left hemiscalp.

Grand averages comparing the session effect in the placebo and risperidone groups are shown in figures 4 and 5. Scalp interpolated maps of the session effect are shown in figure 6. A main effect of session was observed at each electrode subset (sagittal: ($F(1,66)= 26.7$; $p<.001$), parasagittal: ($F(1,66)= 25.1$; $p<.001$), and lateral: ($F(1,66)= 15.2$; $p<.001$)). N400 amplitudes were more negative in the second than the first session. Session x electrode interactions at sagittal ($F(3,198)= 7.3$; $p=.004$) and parasagittal ($F(6,396)= 3.6$; $p=.05$) subsets revealed that this session effect is maximal at anterior electrode sites. In the sagittal subset, a session x electrodes x schizotypy interaction was observed ($F(3,198)= 3.5$; $p=.048$). Here, posthoc analysis revealed that the session difference was maximal at the anterior electrodes of the high but not low schizotypy group. A session x hemiscalp x treatment group interaction was observed at parasagittal electrodes ($F(1,66)= 11.3$; $p=.001$). Posthoc analysis revealed that while the session difference was significant in both risperidone medicated and placebo group, it was significantly larger over the right than left hemiscalp in the risperidone medicated group only. Similarly, a session x hemiscalp interaction was observed in the lateral subset ($F(1,66)= 6.1$; $p=.016$) and posthoc analysis revealed that this session difference was larger over the right than the left hemiscalp.

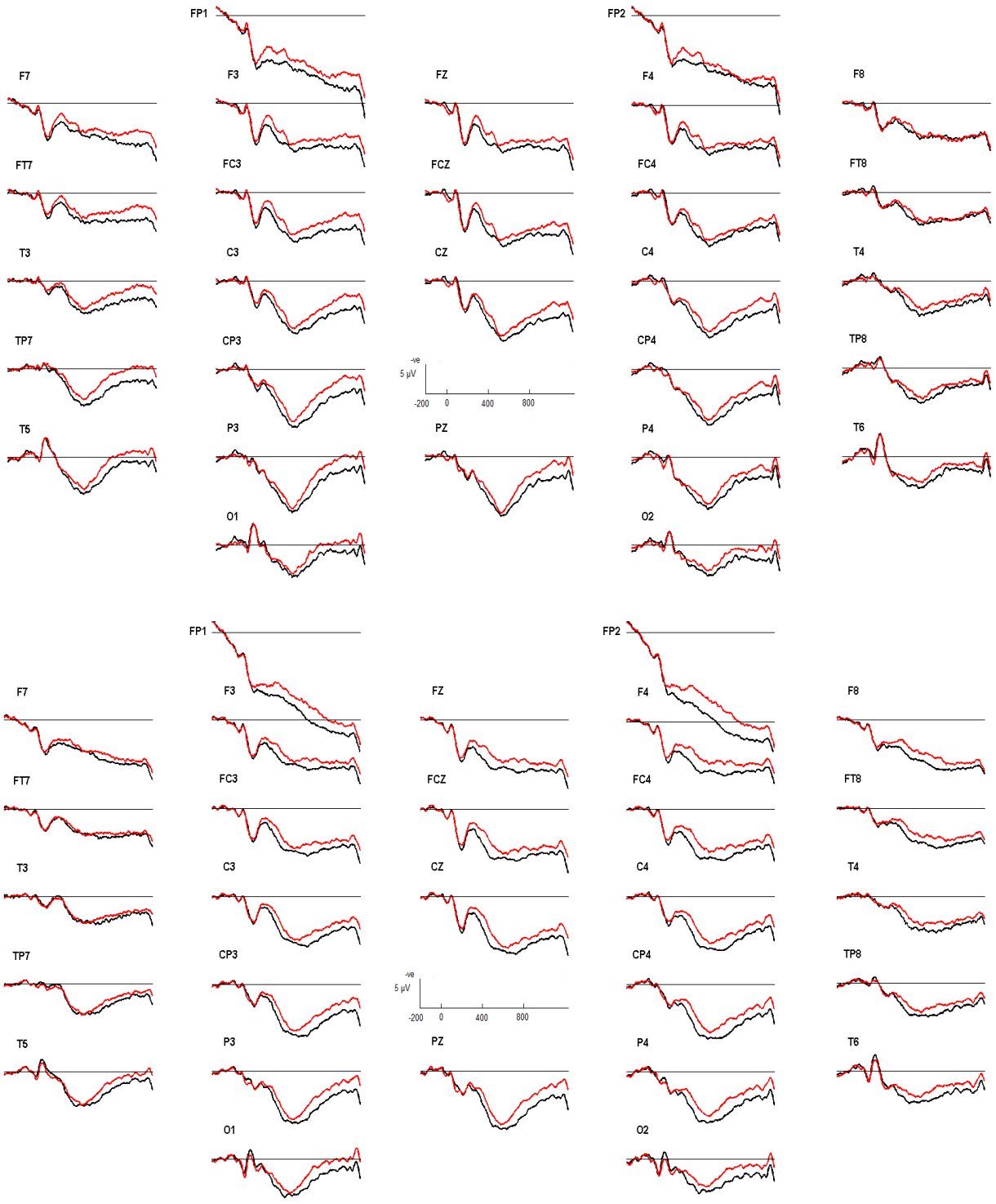

Figure 4. Effect of session in the placebo group (top; n=26) and the risperidone medicated group (bottom; n=44) in the match condition of the semantic categorization task. Black corresponds to the first session and red to the second session.

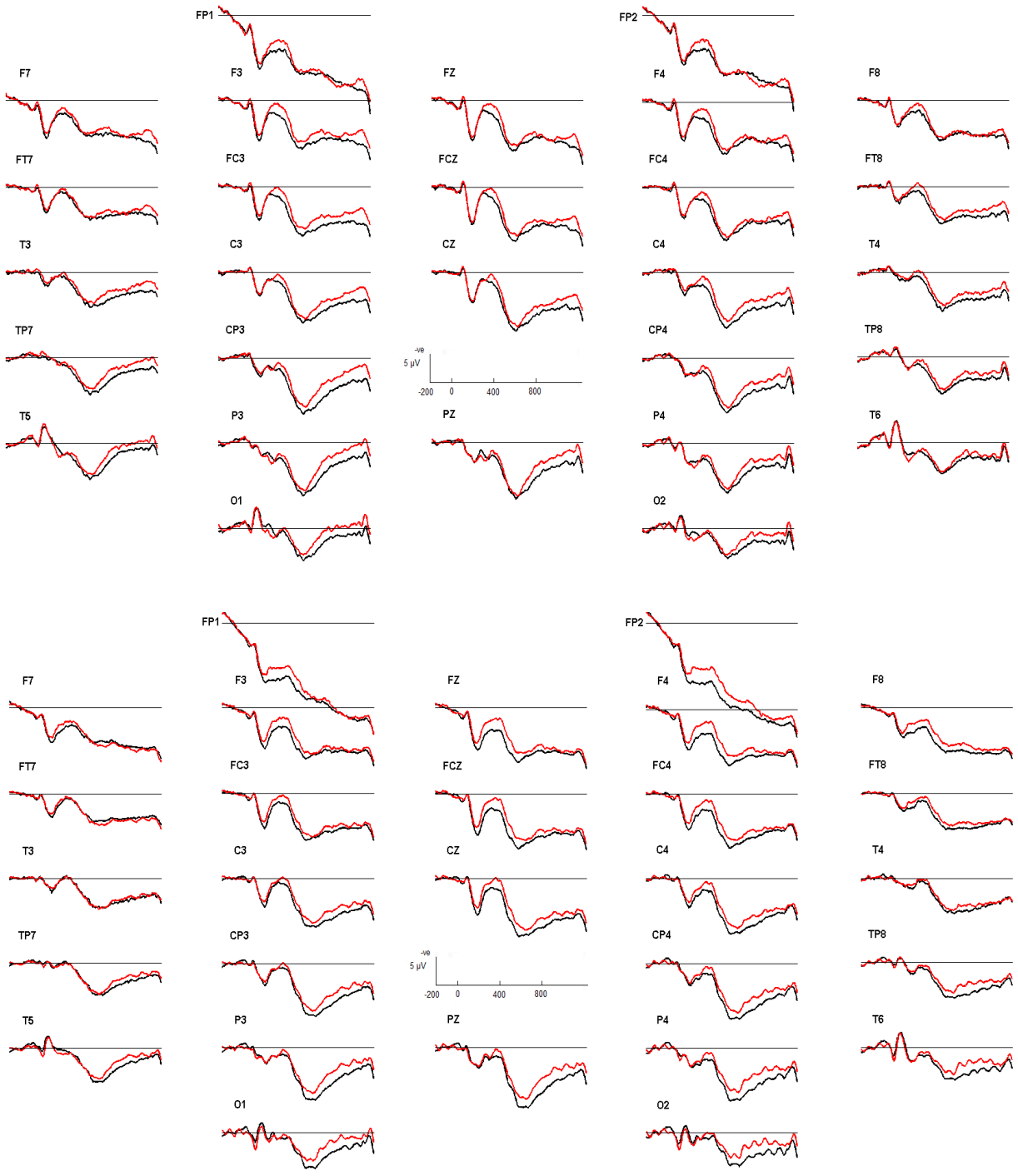

Figure 5. Effect of session in the placebo group (top; n=26) and the risperidone medicated group (bottom; n=44) in the mismatch condition of the semantic categorization task. Black corresponds to the first session and red to the second session.

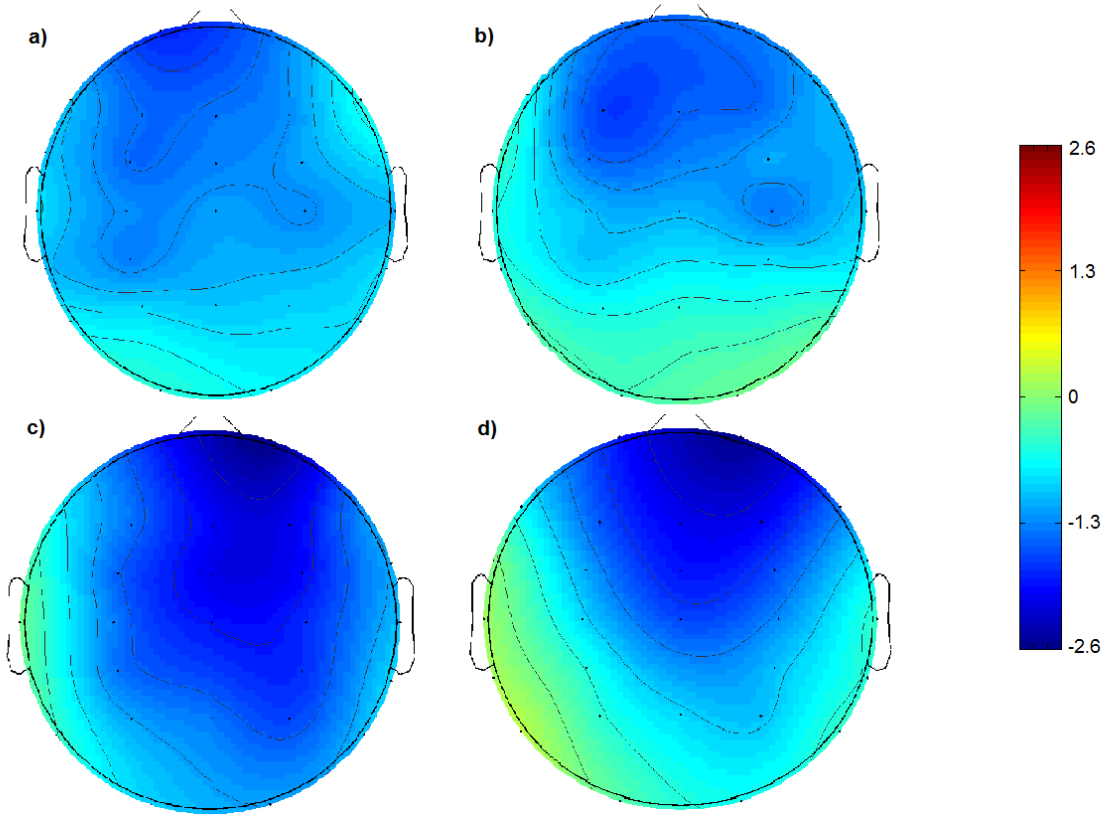

Figure 6. Scalp interpolated maps of the session difference in the a) placebo group in the match condition, b) placebo group in the mismatch condition, c) risperidone group in the match condition and d) risperidone group in the mismatch condition.

3.2 Experiment 2: Social Role Acceptance task

Participants with reaction times shorter than 300 ms or longer than 2000 ms were excluded from this analysis. A minimum of 50 trials to be accepted during averaging was required to retain the participant. A total of 63 participants thus remained: risperidone medicated and high SPQ score= 17; risperidone medicated and low SPQ score= 19; placebo and high SPQ score= 16; placebo and low SPQ score= 11. For role categories where no roles were accepted, reaction times were estimated by calculating the average reaction time for all role categories in that session for each participant.

3.2.1 *Questionnaire measures*

Table 2 shows the demographic and clinical characteristics of the participants included in the social role acceptance task, comparing those with high and low schizotypy and those taking risperidone and those taking placebo. A t-test revealed no significant differences between the risperidone and placebo groups in the mean global SPQ score ($t(61)= -1.8$; $p=.315$) or the mean total PDI score ($t(59)= -2.1$; $p=.700$). Furthermore, global SPQ and PDI scores significantly correlated for all participants (pearson r= .81; $p=<.001$). Repeated measures ANOVA on the STAI revealed that regardless of schizotypy or treatment group, anxiety scores increased from the first (33.7, +/- 6.6) to the second (35.5, +/- 8.4) session ($F(1,55)= 4.4$; $p=.04$). Participants in both the risperidone and the placebo treatment groups reported significantly: lower energy levels ($F(1,59)= 49.3$; $p<.001$), increased sleepiness ($F(1,59)= 14.1$; $p<.001$), less crowded thoughts ($F(1,59)= 4.4$; $p=.04$), less sharp thoughts ($F(1,59)= 43.1$; $p<.001$), more distraction ($F(1,59)=11.7$; $p=.001$), lower current mood ($F(1,59)= 40.4$; $p<.001$) and less intense mood ($F(1,59)= 5.9$; $p=.018$) at the end of the testing day compared to the beginning. Only risperidone medicated participants reported significantly slower thoughts ($F(1, 34)= 25.9$; $p<.001$) and less influence of their thoughts on their current mood ($F(1,34)= 16.2$; $p<.001$). Schizotypy had an influence on ratings of the influence of thoughts on current mood scale, where only the high schizotypy group reported significantly less influence of their thoughts on current mood ($F(1,31)= 14.6$; $p=.001$). Independent sample t-test showed no significant differences between

the placebo and medication groups in any of the side effects commonly associated with risperidone.

	Risperidone medicated group N= 36		Placebo group N=27	
	High SPQ N=17	Low SPQ N=19	High SPQ N=16	Low SPQ N=11
	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)	Mean (S.D.)
Mean age	25.3 (3.3)	23.7 (2.8)	21.9 (2.7)	23.4 (2.8)
Numbers of years of study	14.6 (1.4)	14.8 (1.3)	15.2 (1.8)	14.9 (2.0)
Mean global SPQ scores	35.1 (10.0)	11.1 (6.3)	40.5 (13.3)	14.1 (7.2)
Mean scores for cognitive-perceptual cluster of SPQ	8.4 (3.1)	2.6 (3.1)	9.3 (3.4)	4.7 (3.8)
Mean scores for interpersonal cluster of SPQ	15.0 (8.5)	4.4 (3.8)	17.1 (7.4)	5.3 (4.2)
Mean scores for disorganization cluster of SPQ	8.5 (3.5)	3.2 (2.9)	9.8 (4.1)	2.7 (2.0)
Mean total PDI scores	9.6 (3.3)	2.7 (2.1)	10.4 (4.5)	5.9 (3.4)

Table 2. Demographic and clinical characteristics of the risperidone medicated and placebo groups included in the social roles acceptance task

3.2.2. *Behavioral results*

For percentage of accepted roles, the repeated measures ANOVAs revealed a main effect of each role category: ordinariness ($F(1,59)= 146.4$; $p<.001$) and advantageousness ($F(1,59)= 185.6$; $p<.001$). Participants accepted more ordinary than extraordinary roles (50.6 %, +/- 16.4 vs. 28.5 %, +/- 17.4) and more advantageous than disadvantageous roles (49.8 %, +/- 17.0 vs. 29.4 %, +/- 15.7). Additionally, an ordinariness x advantageousness interaction was observed ($F(1,59)= 17.0$; $p<.001$). As shown in figure 7, ordinary advantageous roles were accepted more than ordinary disadvantageous, which were accepted more than extraordinary advantageous roles and these were accepted more than extraordinary disadvantageous roles (62.4 %, +/- 17.2 vs. 38.9 %, +/- 18.3 vs. 37.1 %, +/- 21 vs. 19.9 %, +/- 15.7, respectively). An ordinariness x schizotypy interaction was also observed ($F(1,59)= 8.1$; $p=.006$). Here, posthoc analysis revealed that participants with high schizotypy accepted significantly more extraordinary roles than those with low schizotypy (34.2 %, +/- 23.2 vs. 22.8%, +/- 25.9), but these groups did not differ significantly in the percentage of ordinary roles accepted, shown in figure 8. Further, an advantageousness x session interaction was observed ($F(1,59)= 4.2$; $p=.046$) and posthocs showed that only favorable roles were accepted significantly less in the second than the first session (47.8 %, +/- 19.3 vs. 51.7 %, +/- 16.9). A session x schizotypy interaction was also observed ($F(1,59)= 5.6$; $p=.022$). Additional analyses showed that participants in the high schizotypy group accepted significantly less roles in the second session (45.5 %, +/- 19.6 vs. 39.8 %, +/- 23.7) but no significant change was observed in the low schizotypy group.

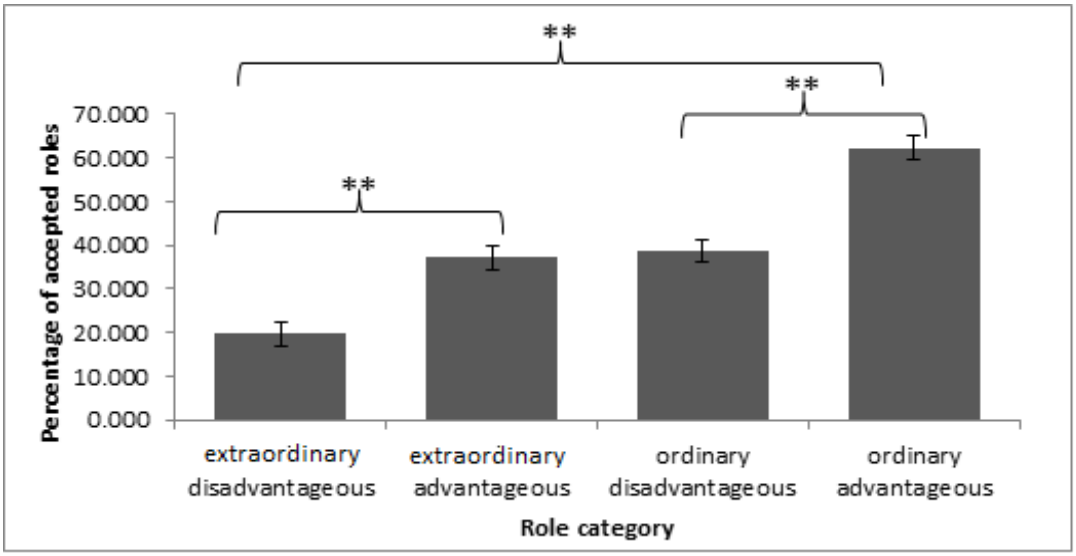

Figure 7. Percentage of accepted roles according to their ordinariness and advantageousness

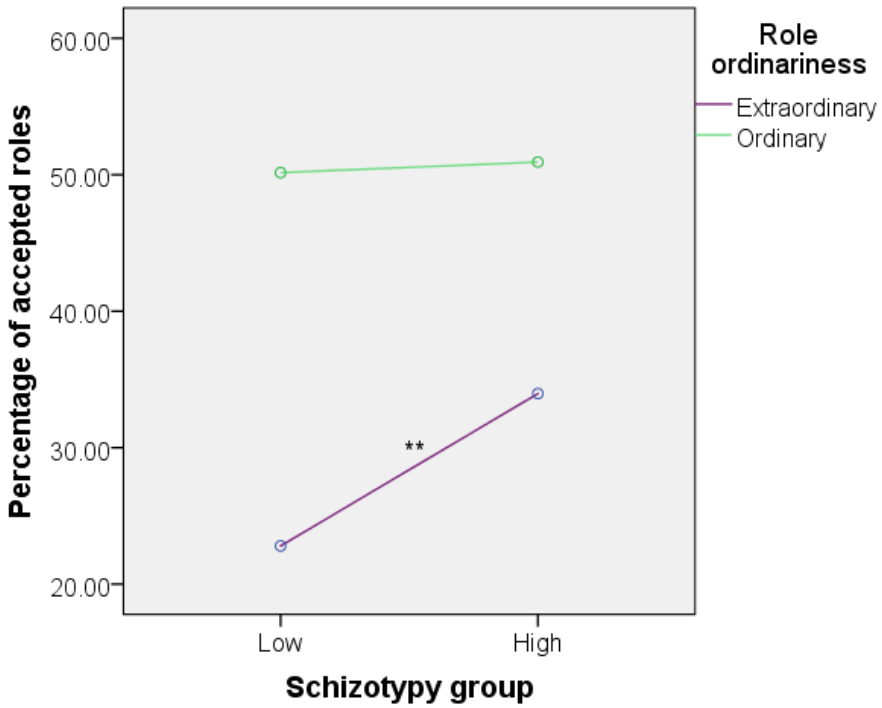

Figure 8. Percentage of accepted roles according to schizotypy

For reaction times, ANOVAs revealed a main effect of each role category: ordinariness ($F(1,59)= 8.0$; $p=.006$) and advantageousness ($F(1,59)= 8.4$; $p=.005$). Time taken to respond to extraordinary roles was shorter than time taken to respond to ordinary roles (985.5 ms, +/- 198.9 vs. 1001.5 ms, +/- 202.7). For advantageousness, reaction times for disadvantageous roles were longer than those of advantageous roles (1001.0 ms, +/- 202.1 vs. 986.1 ms, +/- 199.0). Additionally, ANOVAs revealed decision x ordinariness ($F(1,59)= 17.3$; $p<.001$) and decision x advantageousness ($F(1,59)= 21.6$; $p<.001$) interactions, shown in figures 9a and 9b. Participants were significantly faster to reject extraordinary than ordinary roles (965.5 ms, +/- 203.0 vs. 1007.0 ms, +/- 214.5) but there were no differences in time taken to accept either category. Conversely, participants were significantly faster to accept advantageous than disadvantageous roles (980.5 ms, +/- 197.0 vs. 1021.4 ms, +/- 212.1) but there no differences in time taken to reject either category. Decision and ordinariness further interacted with treatment group ($F(1,59)= 6.7$; $p=.012$). Here, only the risperidone medicated group were significantly faster at rejecting extraordinary than ordinary roles (985.9 ms, +/- 261.6 vs. 1042.5 ms. +/- 284.3; $p<.001$). Also, this group was significantly faster at accepting ordinary than extraordinary roles (1023.7 ms, +/- 264.4 vs. 1048.3 ms, +/- 273.5; $p= .013$).

A session x ordinariness x schizotypy interaction ($F(1,59)= 4.1$; $p=.048$) showed that only the high schizotypy group, but not the low, was faster at responding to ordinary roles in the second than the first session (942.0 ms, +/- 155.7 vs. 976.6 ms, +/- 152.3; $p= .017$), and there was no significant difference in time taken to respond to extraordinary roles. Schizotypy further interacted with decision ($F(1,59)= 5.4$; $p=.023$) and post hoc analysis revealed that participants with high schizotypy were faster to accept roles than those with low schizotypy (948.8 ms, +/- 270.4 vs. 1053.4 ms, +/- 301.2; $p= .045$), but there was no significant difference between the two groups in time taken to reject roles. Finally, we observed a session x treatment group x schizotypy interaction ($F(1,59)= 7.6$; $p=.008$), where reaction times of the placebo high schizotypy group only decreased significantly from the first to the second session (924.9 ms, +/- 208.7 vs. 846.8 ms, +/- 209.2).

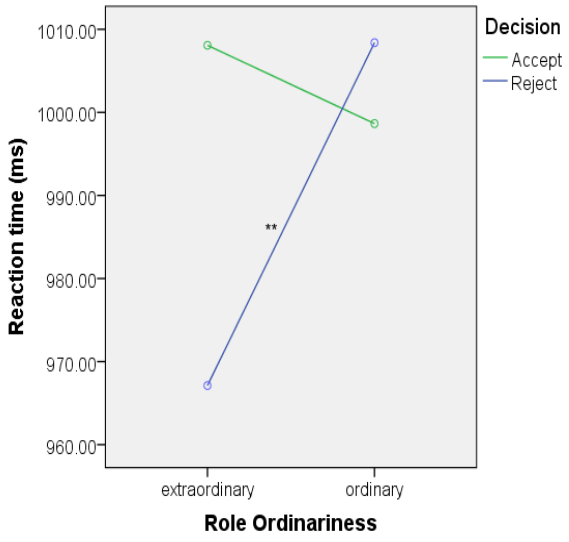

Figure 9a. Reaction times according to role ordinariness and decision

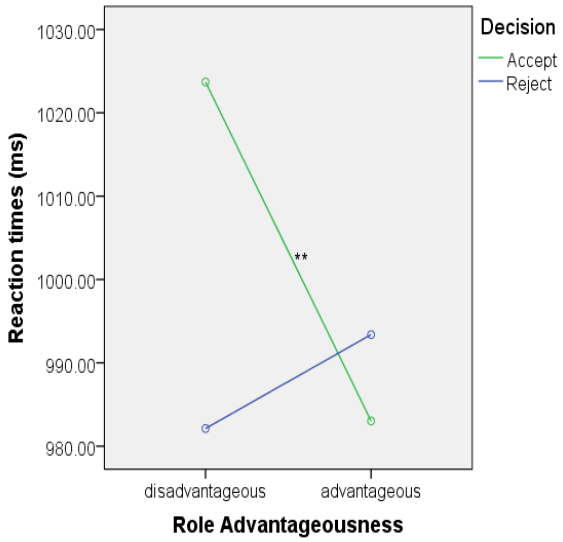

Figure 9b. Reaction times according to role advantageousness and decision

3.2.3 *ERP results – 250-550 ms time window*

In the 250-550 ms time window, ANOVAs revealed a main effect of decision at the sagittal ($F(1,59)= 9.2$; $p=.004$) and parasagittal ($F(1,59)= 5.6$; $p=.021$) electrode subsets. ERPs were more negative when rejecting a role than when accepting it. A decision x electrode x treatment group x schizotypy interaction was also observed at parasagittal electrodes ($F(6, 354)= 3.2$; $p=.027$). Here, the effect of decision was significant only for the low schizotypy placebo group ($F(1,10)=5.4$; $p=.043$) at the following electrodes: F3/4 ($F(1,10)=8.4$; $p=.016$), C3/4 ($F(1,10)=5.3$; $p=.045$), Cp3/4 ($F(1,10)=7.1$; $p=.023$), P3/4 ($F(1,10)= 5.5$; $p=.041$). N400 amplitudes were more negative for rejected than accepted roles.

Grand averages comparing the session effect in the placebo groups are shown in figures 10 and 11. Scalp interpolated maps of the session effect in the 250-550 ms time window are shown in figure 12. While ANOVAs did not yield a main effect of session at any of the electrode subsets, a session x electrode interaction was observed: sagittal ($F(3,177)= 13.3$; $p<.001$); parasagittal ($F(6,354)= 17.5$; $p<.001$) and lateral ($F(4,236)= 21.6$; $p<.001$). Posthocs revealed

that the effect of session was significant at centroparietal and temporal sites (Cz, Pz, C3, C4, Cp3, Cp4, P3, P4, Tp7, Tp8, T5 and T6) where N400 amplitudes were less negative in the second than the first session. Additionally, the effect of session was significant at frontal sites (i.e., Fp1, Fp2, F7 and F8) but here, N400 amplitudes were more negative in the second compared to the first session.

At the parasagittal and lateral electrodes, a session x hemiscalp x treatment group interaction was further observed (parasagittal ($F(1,59)= 10.0$; $p=.002$); lateral ($F(1,59)= 4.5$; $p=.038$)). Post hoc analyses showed a session x hemiscalp interaction for the risperidone medicated group only (parasagittal: $F(1,34)= 6.9$; $p=.013$); lateral: ($F(1,34)= 9.6$; $p=.004$)). The session effect reached significance only in the lateral electrodes of the left hemiscalp ($F(1,34)= 7.9$; $p=.008$), where mean N400 amplitude was less negative in the second than the first session.

3.2.4 *ERP results – 600-1000 ms time window*

In the 600-1000 ms time window, ANOVAs revealed a main effect of decision only at lateral electrodes ($F(1,59)= 4.1$; $p=.047$) where the amplitude of this component was more positive for rejected than accepted roles. However, decision x schizotypy interactions were observed at all electrode subsets: sagittal ($F(1,59)=8.3$; $p=.005$); parasagittal ($F(1,59)= 8.1$; $p=.006$); and lateral ($1,59)= 10.7$; $p=.002$). Posthocs showed that the effect of decision was significant only for the high schizotypy group (sagittal: ($F(1,31)= 5.3$; $p=.028$); parasagittal ($F(1,31)= 6.4$; $p=.017$); lateral ($F(1,31)= 11.7$; $p=.002$). The amplitude of this late positive component was more positive for rejected than accepted roles in this group.

Scalp interpolated maps of the session effect in the 600-1000 ms time window are shown in figure 13. ANOVAs revealed main effects of session at the sagittal ($F(1,59)= 11.1$; $p=.001$) and parasagittal ($F(1,59)= 7.1$; $p=.01$), but not lateral, electrode subsets. Here, the amplitude of the LPC was more positive in the second than the first session at both electrode subsets. Additionally, a session x decision x electrodes interaction was observed at lateral electrodes ($F(4,236)= 3.2$; $p=.049$) and post hoc analysis revealed that the LPC was more positive in the second than first session for rejected roles only, at Ft7/8 ($F(1,59)= 5.8$; $p=.019$) and T3/4 ($F(1,59)= 6.5$; $p=.014$).

A session x electrodes x hemiscalp x treatment group interaction was observed at parasagittal electrodes ($F(6, 354)= 2.7$; $p=.038$, epsilon= .584). The session x electrodes x hemiscalp was significant only for the risperidone medicated group ($F(6,204)= 4.1$; $p= .008$). In this group, the amplitude of the LPC increased in the second session at both hemiscalps (left: ($F(1,34)= 10.1$; $p=.003$); right: ($F(1,34)= 6.1$; $p=.019$)). This increase was larger over the left than right hemiscalp (1.165 µv vs. 0.880 µv) and was significant at all electrodes in this subset (all ps<.05). At lateral electrodes, a session x hemiscalp x treatment group interaction was observed ($F(1,59)= 8.3$; $p=.005$). Post hoc analysis revealed that the session x hemiscalp interaction was significant in the risperidone medicated group only ($F(1,34)= 6.1$; $p= .019$). For these electrodes, the increase in the LPC was observed only in the left hemiscalp for the risperidone medicated group ($F(1,34)= 9.1$; $p=.005$).

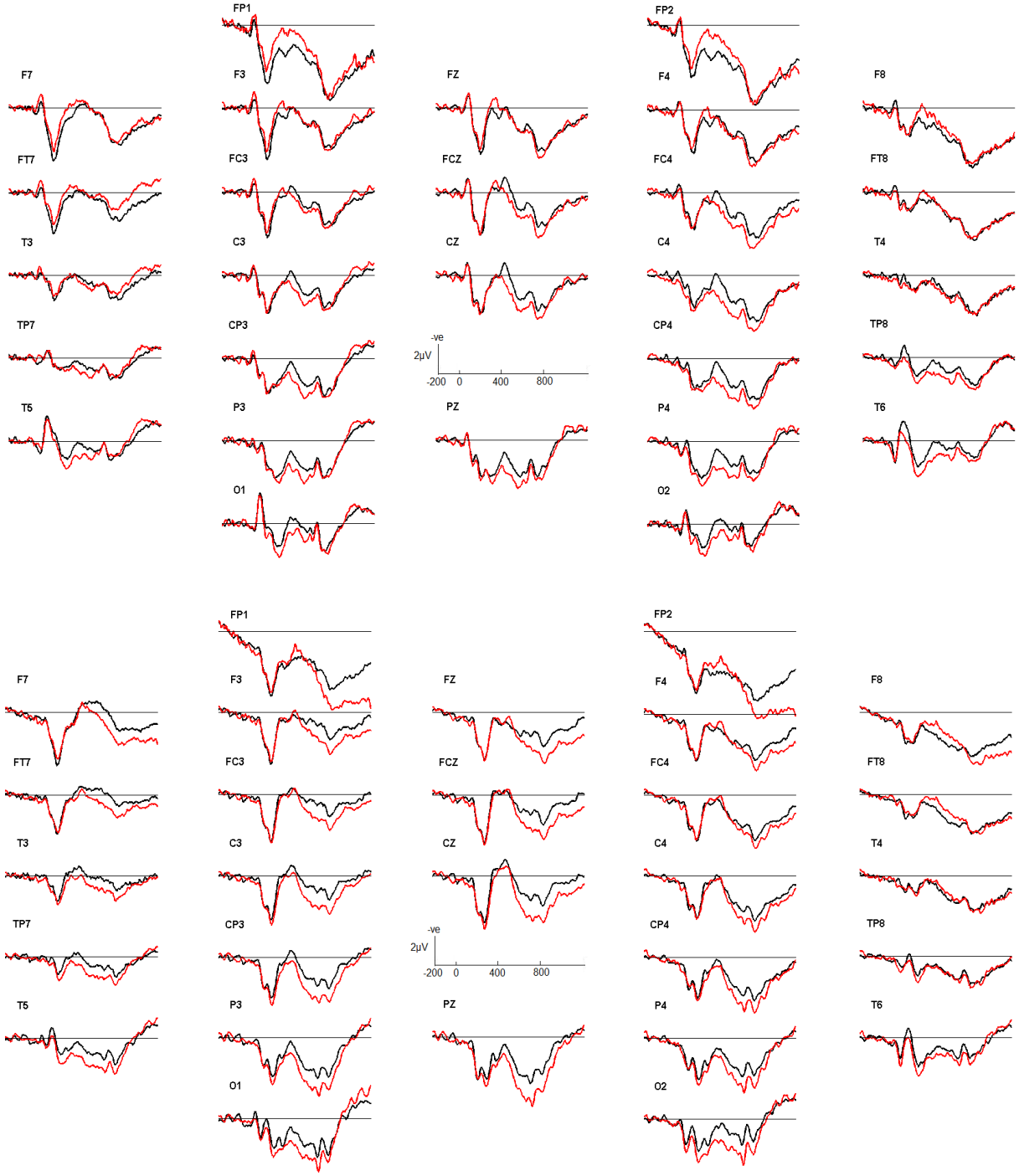

Figure 10. Effect of session in the placebo group (top; n=27) and the risperidone medicated group (bottom; n=36) for *accepted roles* in the social role acceptance task. Black corresponds to the first session and red to the second session.

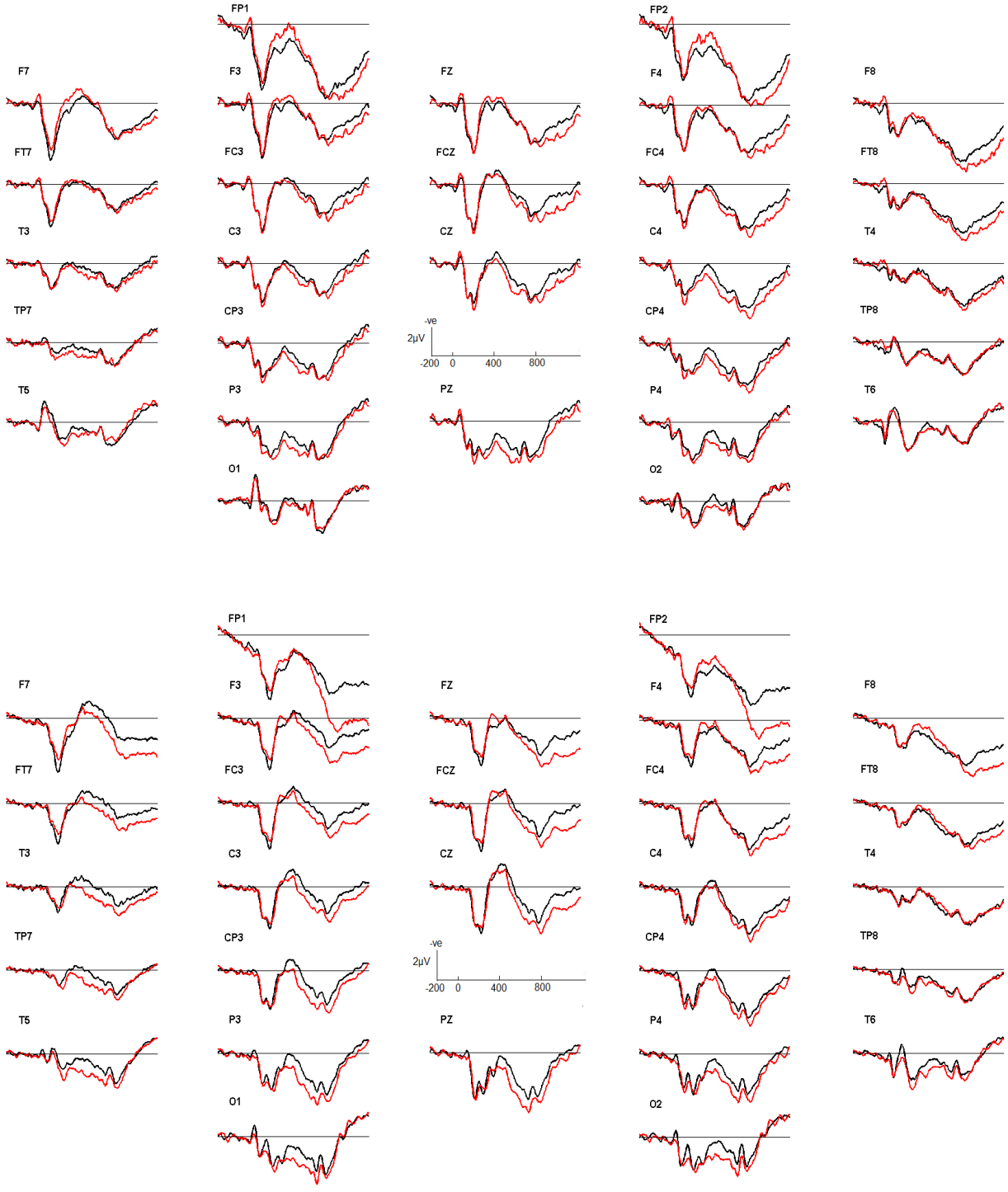

Figure 11. Effect of session in the placebo group (top; n=27) and the risperidone medicated group (bottom; n=36) for *rejected roles* in the social role acceptance task. Black corresponds to the first session and red to the second session.

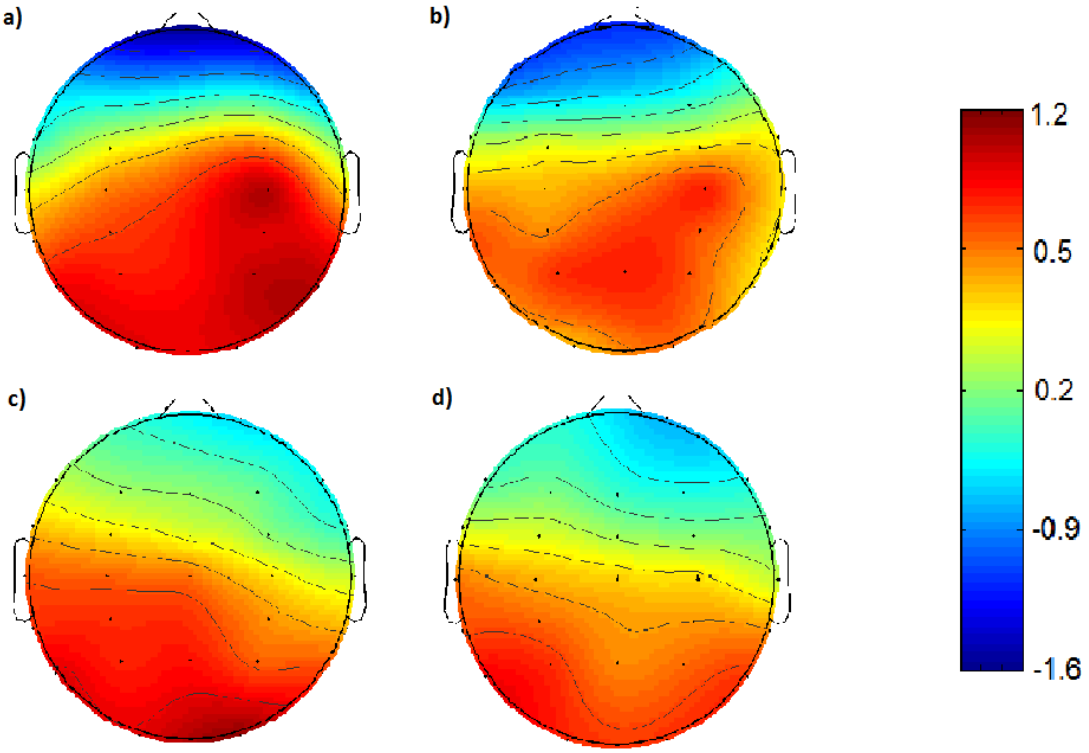

Figure 12. Scalp interpolated maps of the session difference (session2-session1) at the 250-550 ms time window in the **a)** placebo group for accepted roles, **b)** placebo group for rejected roles, **c)** risperidone group for accepted roles and **d)** risperidone group for rejected roles.

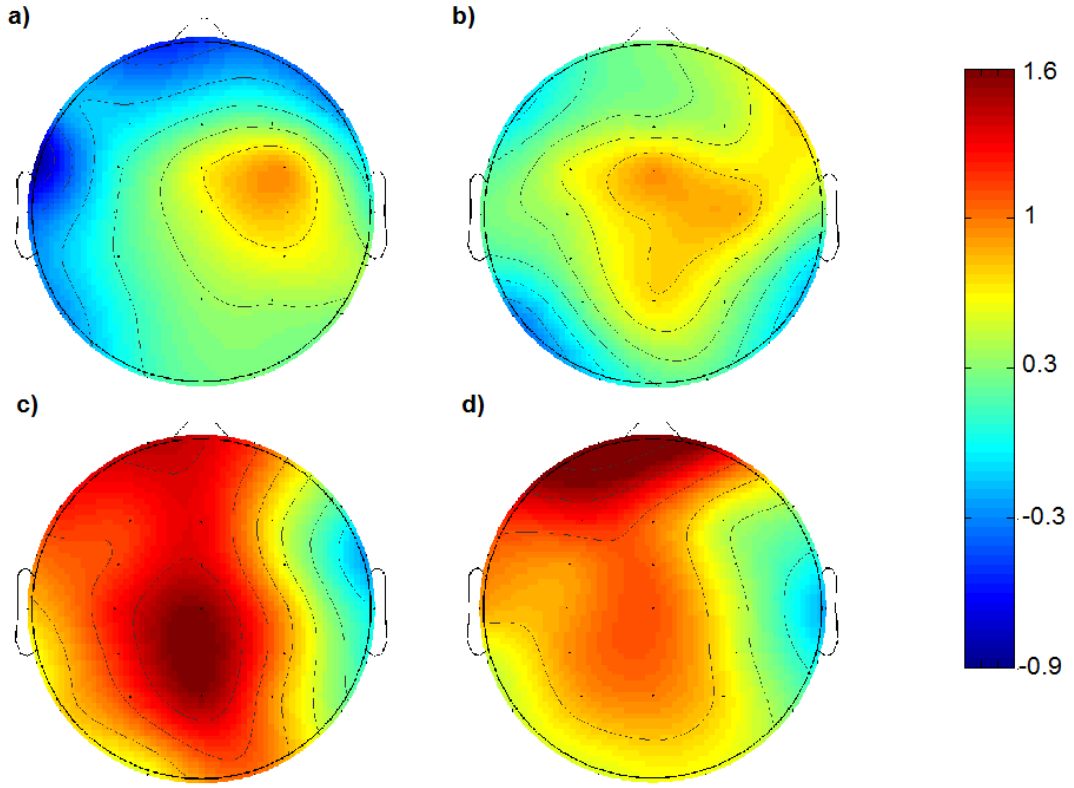

Figure 13. Scalp interpolated maps of the session difference (session2-session1) at the 600-1000 ms time window in the **a)** placebo group for accepted roles, **b)** placebo group for rejected roles, **c)** risperidone group for accepted roles and **d)** risperidone group for rejected roles.

4. *Discussion*

The present study primarily investigated the effect of risperidone on the N400, in order to determine whether the therapeutic effect of antipsychotic medications is brought about by their action on the neural networks involved in semantic processing. In order to avoid confounds that are associated with using schizophrenic patients, such as previous medication use, healthy volunteers were used. Participants performed two tasks shown to elicit the N400: the commonly used semantic categorization task and a novel more ecologically valid social role acceptance task. We further divided participants according to their schizotypy to study its influence on the performance of these tasks and to determine whether the degree of schizotypy could have an impact on the medication effect. We hypothesized that risperidone, will produce an immediate reduction in the N400 component in the semantic categorization task, consistent with the delayed effect of olanzapine previously observed. We further hypothesized that due to the semantic nature of the social role stimuli and the involvement of the self in their processing, risperidone will have an impact on the N400s and LPCs evoked by these stimuli.

4.1. *Semantic Categorization task*

First, the effects of schizotypy on the well-established centro-parietal N400 effect are worth reporting. N400 amplitudes elicited by incongruent target words were more negative than those elicited by congruent target words. Consistent with classic N400 priming effect, this difference was maximal at centro-parietal sites and was observed for both schizotypy and treatment groups. Additionally, we observed hemispherical differences for this effect, where it was larger over the right than left hemiscalp, regardless of schizotypy and treatment. According to Federmeier and Kutas (1999), the left hemisphere contributes to prediction generation based on the semantic category and compares the presented target to it. Processing of shared semantic properties is then facilitated by the contribution of the left hemisphere. In contrast, the right hemisphere contributes to integration with context, where the semantic features of a presented stimulus are compared against representations maintained in working memory and any violation of the context maintained in working memory elicits the contribution of the right hemisphere (Federmeier & Kutas, 1999). In this paradigm, the contribution of the right hemisphere is

dominant due to the absence of target words that share semantic features in the two conditions (i.e., the target word is either an animal or object name). The constancy of the context (i.e., the prime in the condition that requires a response is always of the "animal" category) further constraints left hemisphere contribution by limiting generated predictions. Together, these explain the larger mismatch-match difference observed over the right than left hemiscalp in this study.

Consistent with the literature on the N400 and schizotypy, the difference in the N400 amplitude elicited by the incongruous target and of that elicited by the congruous target was observed to be smaller in participants with high schizotypy, compared to those with low schizotypy. Because we analyzed raw N400s as opposed to difference waves, we were further able to determine that N400 effect reduction was due to smaller N400s elicited by the incongruous target in addition to larger N400s elicited by the congruous target in the high than low schizotypy groups. These N400 differences between the schizotypy groups further support the idea of deficits in semantic memory processing in schizotypy. In high schizotypy, the activation of unrelated words with the presentation of the prime that would require less integration effort would explain in the smaller N400 amplitudes observed in the mismatch condition. For related targets, larger N400s than in low can then be explained by deficits in activation spread to the related representations, thus more integration effort is required. Similarly, these effects can be explained from an inhibition perspective (de Loye, Beaucousin, Bohec, Blanchet, & Kostova, 2013; Debruille, 1998; Debruille, 2007). The longer SOAs used in the current paradigm allow for controlled processes that involve the generation of predictions and then integrating those into the established context. In high schizotypy individuals, the automatic activation of unrelated targets would require less inhibitory processes when the incongruent target appears and more inhibitory processes of unrelated representations when the congruent target appears. Additionally, the absence of hemispherical differences between the high and low schizotypy groups in this task is consistent with the idea that the functional asymmetry of the two hemispheres is preserved in schizotypy during language processing (Kostova et al., 2013). These deficits, specific to implicit memory function (Morgan et al., 2009), further provide an explanation for the endorsement of abnormal beliefs in this population.

Although there was no significant difference in SPQ scores, ERP differences were observed between the placebo and risperidone medicated groups. Here, the placebo group was found to have larger mismatch-match differences than the risperidone group. Specifically, the N400s elicited by in the match condition in the former group were smaller than those elicited by the risperidone medicated group while the N400s elicited in the mismatch condition were not significantly different. As the design of the current experiment was not a crossover design, this observation could be reflective of individual differences between participants. As there was no interaction with session, it is unlikely that this is an effect of the experimental manipulation.

An increase in the N400 amplitude was observed across sessions for both the medication and placebo groups and the maximal differences were observed at frontal sites. Because the N400s significantly changed in the placebo group, the specific effect of risperidone on this ERP component should be interpreted with care and a possible impact of task training on the N400 should be mentioned.

In ERP investigations of recognition memory, modulations by familiarity of fronto-central ERPs in the 300-550 ms time window have been reported (Wolk et al., 2004). Familiarity is described as a recognition memory process that represents a vague sense of previous encounter which facilitates processing, or increases fluency. Fluency modulations behave similarly to N400 priming effects, where it attenuates the fronto-central N400 amplitudes reflecting the ease of processing (Tsivilis, Otten, & Rugg, 2001). The augmented fronto-central N400 amplitudes observed in the current task in the placebo group could be explained by two ideas. Firstly, as the specific items were not repeated across sessions, we suggest that conceptual familiarity is in play, specifically relating to either the animal or object concepts that are continuously activated. Secondly, the onset of the prime in the second session would activate a greater spread of activations than that of the first session due to the previous occurrence of a wider range of target words after that prime, further influenced by prime repetition in this paradigm. Violations of generated predictions of target words that appeared in the first session together with greater inhibition required for that greater spread of activations would explain the greater N400 amplitudes observed in the second session of the placebo group, despite task familiarity. Reaction times remained unaffected across sessions, which could be accounted for by the ease of predicting target words due to continuous presentation of the prime in addition to the need for

greater inhibition brought about by the greater activation of representations in the second session. These two acting against each other could lead to constant reaction times across sessions. Alternatively, participant motivation has previously been reported to influence event-related potentials. While session effects on the N400 have not been studied before, Kiang et al. (2013) report a similar effect on related targets only (Kiang, Patriciu, Roy, Christensen, & Zipursky, 2013). Here, authors attribute this increase to reduced motivation and participant involvement in the task. In particular, Kiang et al. (2013) suggest that due to reduced motivation, participants fail to use the prime to predict target words, accounting for the increase in N400 amplitudes across sessions. However, the authors do not provide an account for why this effect is only seen with related targets but not unrelated target words. It is important to note that in that study, the second testing session was done a week after the first, while in the present study it was done after 90 minutes of the first session. This difference in time elapsed between sessions could explain the increase of the N400 amplitude for related targets only. Together, these data provide another possible modulator of the N400 amplitude and additionally support the presence of inhibitory processes that are indexed by this ERP.

A differential effect of session on each hemiscalp was observed in the risperidone medicated group, where a larger increase of the frontal N400 was observed over the right than the left hemiscalp. Due to the hypothesized influence of session on the frontal N400, it is difficult to determine from this data whether risperidone produces an immediate increase or, like olanzapine (Debruille et al., 2013), a decrease of this ERP component. Risperidone could produce an immediate increase over the right hemiscalp in addition to the increase brought about by session, but leave the left hemiscalp unaffected. Alternatively, the medication could *decrease* frontal N400 amplitudes over the left hemiscalp but leave the right hemiscalp unaffected. This, in combination with the increase due to session, would result in the observed increase over the right than left hemiscalp. It is also possible that risperidone produces an increase in the right hemiscalp *in addition to* a decrease over the left hemiscalp to produce the observed effects. It has been shown that dopamine increases semantic focusing by inhibiting the spread of activations within semantic memory in healthy volunteers (Copland et al., 2009; Kischka et al., 1996). Furthermore, using a lateralized stimulus presentation paradigm, Roesch-Ely et al. (2006) showed that these effects of dopamine agonists are specific to frontal areas within the left hemisphere (Roesch-Ely et al., 2006). Taking schizotypy into account, Mohr et al. (2005) report

that L-dopa administration improved performance of the left hemisphere, with a lack of contribution of the right hemisphere, specifically with increasing scores in measures of negative schizotypy. In line with this data, we propose that risperidone primarily affected processes within the left hemiscalp, where it decreased the N400 due to reduced inhibitory effects brought about by its dopamine receptor antagonism, opposite to the effects observed with dopamine agonists. A lateralized stimulus presentation paradigm as in Federmeier & Kutas (1999) and de Loye et al. (2013) could be used to further confirm this.

While the results of the present study are inconclusive in terms of the effect of risperidone on the N400 as an index of semantic processing, they provide support for ERP differences with respect to schizotypy. Furthermore, they suggest an influence of practice effects and session on the N400 component that is present 90 minutes following first encounter. Finally, we propose that the subtle effect of risperidone is lateralized and seems to be in the same direction as that of olanzapine, reducing the N400 amplitude.

4.2. *Social Roles Acceptance task*

The social roles acceptance task is a novel task with high ecological validity which was designed to assess decision making processes for choices encountered in everyday life. The purpose of introducing this task is to investigate the influence of schizotypy on perceptions of social role fit within the self-concept, to further understand the increasing social deficits observed along the schizotypy continuum. We further aimed to determine the effect of antipsychotics on the neural substrates involved in the processing of these stimuli. Due to the semantic nature of social role stimuli, we predicted modulations of the N400 amplitude according to whether a role was accepted or rejected. Given the involvement of decision evaluations, we suggest that a later ERP component, the LPC, will also be elicited and modulated by evaluations of personal suitability.

Before discussing the influence of schizotypy and antipsychotics on decision and reaction times, the general patterns of responding to social roles in a general young adult population are worth mentioning. Firstly, we observed a gradient in the percentage of roles accepted depending on their category. Ordinary advantageous roles were accepted more frequently than ordinary

disadvantageous roles, which were accepted more frequently than extraordinary advantageous roles and finally extraordinary disadvantageous roles were accepted least frequently. Secondly, extraordinary roles in general were rejected significantly faster than ordinary ones, while advantageous roles were accepted significantly faster than disadvantageous roles. Together, this data suggests that the decision to accept a role seems to be driven by advantageousness judgements while decisions to reject a role are driven by ordinariness judgements.

With respect to schizotypy, we observed that individuals in the high schizotypy group accepted significantly more extraordinary roles than those in the low schizotypy group but no significant difference was observed for ordinary roles. This effect of schizotypy was not observed for roles according to their advantageousness. Moreover, high schizotypy was associated with significantly shorter reaction times when accepting roles compared to low schizotypy, reflecting impulsivity tendencies in high schizotypy (Rim, 1994). The relationship between social role acceptance and perceived characteristics of each role could provide an interesting direction of research to further understand why individuals with high schizotypy endorse extraordinary roles.

In the 250-550 ms time window, a more negative ERP was elicited for rejected than accepted roles, and this effect was not dependent on electrode site. Processing of self-referential semantic information has been observed to be modulated by the emotional valence of the stimuli (Watson et al., 2007). In specific, Watson et al. (2007) showed that N400 amplitudes were larger when self-referential semantic information was of negative nature compared to when it was positive, suggesting that the size of the N400 is sensitive to the discrepancy of semantic information to the individual's self-concept. The present increase in the N400 amplitude to rejected roles can then be explained within this context, where roles discrepant to the self-concept (and thus rejected) elicit a larger N400 than roles consistent with the self-concept (and thus accepted). The absence of modulations on the fronto-central N400s in this task as seen in Watson et al. (2007) can be attributed to the differences in stimuli used. A social role stimulus can be thought of as encompassing representations not limited to the self. For instance it can elicit representations of related objects, related roles, other individuals one knows to play these roles, etc. that would all be automatically activated. Alternatively, the greater N400 observed for rejected roles could reflect the negative valence associated with the extraordinary and

disadvantageous roles that are comprise the rejected roles. In particular, Watson et al. (2007) suggest that processing of self-referential information is influenced by its emotional valence accounting for the modulation of fronto-central N400s. To investigate this with social roles, future experiments could be done to characterize social role valence to the decision to accept or reject the role.

As with the N400s observed in the semantic categorization task, session modulated their amplitudes in the social role acceptance task. Regardless of the decision made, schizotypy or treatment group, an increase in frontal N400s was observed in the second session while centro-parietal N400s decreased in amplitude. This unexpected effect of session could reflect changes in the mental strategy used to perform this task. Decreases in the centro-parietal N400 have been associated with ease of processing, either by stimulus repetition (Kutas & Federmeier, 2011) or reduced spread of automatic activations and thus less inhibition of inappropriate representations (Debruille et al., 2013). Because the context is kept consistent in this task (i.e., suitability with the self-concept), it is possible that task repetition makes processing of the social role word require less activation of semantic networks and more involvement of self-concept representations. This would result in reduced inhibitory processes of unrelated semantic representations and the smaller centro-parietal N400s observed. In addition to more automated semantic processing of the social role stimuli, a greater involvement of prefrontal areas dedicated to the self-concept processing would account for the increase in frontal N400s.

Contrary to our hypothesis, an effect of risperidone on the frontal N400s was not observed. Regardless of the decision made, risperidone decreased N400 amplitudes over the left hemiscalp only, but no statistically significant difference was observed over the right hemiscalp of this group or in the placebo group. This observation would support the second interpretation of the risperidone effect in the semantic categorization task, where it was suggested that it decreases N400 amplitudes over the left hemiscalp and leave the right hemiscalp unaffected. This effect of risperidone is specific to its neurophysiological properties of dopamine receptor antagonism. By increasing dopamine in left hemisphere semantic networks, risperidone would increase focusing of activations and therefore reduce inhibitory processes and this would account for the reductions of the N400 over the left hemiscalp of the risperidone medicated group. Alternatively, the size of the dose could account for this hemispherical effect. It is possible that a

bigger dose might be required to bring about observable electrophysiological differences within right hemisphere semantic networks. In fact, in a positron emission tomography (PET) study investigating the effect of risperidone in healthy volunteers, authors report that a 2 mg dose was necessary for an antipsychotic effect of this medication (Lane, Ngan, Yatham, Ruth, & Liddle, 2004).

We additionally observed that the risperidone effect was present only for the high schizotypy but not low schizotypy participants. This is similar to the effect of olanzapine according to schizotypy reported in Debruille et al. (2013) and is related to baseline differences in dopamine levels within semantic memory networks between the schizotypy groups.

For the late positive component (LPC), greater positivity, peaking at 800 ms, was observed for rejected than accepted roles, only in the high schizotypy group. The LPC has been related to the evaluation of memory contents, or post-retrieval processing, and correlates with activity in the prefrontal cortex (Wolk et al., 2004). In particular, self-referential judgements are observed to elicit more frontal positivity than non-self-referential judgements (Kelley et al., 2002). Furthermore, it is implicated in explicit semantic processing that occur post decision and is thought to reflect a decision evaluation process (Juottonen et al., 1996). Additionally, a more positive LPC, peaking at 700 ms, has been reported in relation to mental imagery (West & Holcomb, 2000). While the influence of schizotypy on this ERP isn't well studied, its modulation by decision in the high schizotypy group only could suggest greater evaluation of the decision to reject a role or greater mental imagery for rejected roles by these participants. Alternatively, this difference could be due to the valence of the roles rejected and accepted by each schizotypy group. Because, the high schizotypy group accepted significantly more extraordinary roles than the low schizotypy group, their rejected roles would consist of the extremely extraordinary roles that would be of negative valence. Stimuli with negative valence have been reported to increase the amplitudes of the late positive component than those with positive valence, reflecting negativity bias in stimulus evaluation (Ito, Larsen, Smith, & Cacioppo, 1998). Further characterization of the valence of the social role stimuli is required to validate this.

Like with the N400, risperidone was observed to affect LPC amplitudes mostly over the left hemiscalp. More positivity was observed in the second session over the left than right

hemiscalp for the risperidone medicated group, but LPC changes in the placebo group were absent. This greater frontal positivity, observed in both schizotypy groups, could reflect a boosting of self-referential decision evaluative processes, perhaps accompanied by greater mental imagery of oneself playing the presented role.

Taken together, the results of this experiment support the schizotypy continuum approach where subtle differences in semantic processing are observed between low and high schizotypy during semantic categorization. Additionally, the endorsement of abnormal beliefs in high schizotypy is further supported by increased acceptance of extraordinary roles by these participants. The effect of the antipsychotic risperidone in healthy individuals appears to be lateralized to the left hemisphere, which is reminiscent of reductions in metabolism in the left lateral frontal cortex reported after a 2 mg dose of risperidone in healthy participants and schizophrenia patients (Lane et al., 2004; Ngan, Lane, Ruth, & Liddle, 2002). Whether this effect reflects neurophysiological effects of the drug or improvements in semantic processing is yet to be elucidated. Finally, the present results point to another factor modulating the N400 amplitude: task training.

4.3. *Limitations*

With respect to the overall design of the experiment, our results are limited by the use of a between-group design as opposed to a cross-over design. While this design allows for an ecologically valid assessment of the effect of antipsychotics on ERPs that can be utilized with patients, baseline between-group differences were observed. Additionally, both risperidone and the placebo were administered at the beginning of the first session and as such we did not obtain real baseline ERP recordings. Because orally disintegrating risperidone was used here, changes in brain chemistry during the first session are probable. It was thus difficult to disentangle group differences from early effects of risperidone. While the use of healthy volunteers over schizophrenia patients allowed for circumventing confounds like disease chronicity and previous antipsychotic use and as such allow for the investigation of the physiological effects of the risperidone molecule, baseline differences in neurochemistry of healthy and diseased brains poses difficulties in translating this research onto the schizophrenia population. As such, it is critical to further examine schizophrenia patients under the current experimental design.

In the social role acceptance task, we were unable to study ERP differences between the role categories and as such were unable to determine whether schizotypy and risperidone had an influence on the processing of each role category. Additionally, we were unable to examine how role categories influence the decision to accept or reject a role. Finally, the unexpected session effects on the N400 introduced a confound that hinders a conclusive interpretation of the effect of risperidone on semantic processing.

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