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Time Course of the Dorsal and Rostral-Ventral Anterior Cingulate Cortex Reveals the Influence of Emotional Valence and Arousal on Cognitive Control in Healthy Subjects and Patients With Schizophrenia

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Partial results of the presented work (Study 1) have been published in (Feroz et al., 2017). Figures 3, 5, 8 to 19 were reprinted, with permission from (Feroz et al., 2017). Copyright 2017 with permission from Springer

Partial results of the presented work (Study 2) have been submitted at:
Feroz, F. S., Leicht, G., Rauh, J., and Mulert, C. The Time Course of dACC and rvACC Activity Reveals Valence and Arousal Aberrant Modulation in Patients with Schizophrenia in the Emotional Stroop Experiment (under review, *Brain Topography*)

1 Introduction

1.1 Background

1.1.1 The dorsal and rostral-ventral ACC

Growing evidence from neuroimaging studies suggest that emotional and cognitive processes are interrelated and integrated in the brain. An anatomical key structure in emotion-cognition tasks is the ACC (Albert et al., 2010; Allman et al., 2001; Kanske and Kotz, 2011b; Stevens et al., 2011; To et al., 2017). One significantly influential view in this area of research (Bush et al., 2000) dichotomizes the ACC into areas that are functionally specialized in cognitive and emotional processing tasks, based on activation patterns found in fMRI studies. Figure 1 illustrates the areas (Bush et al., 2000) within the ACC that are activated and deactivated in cognitive and emotional fMRI studies.

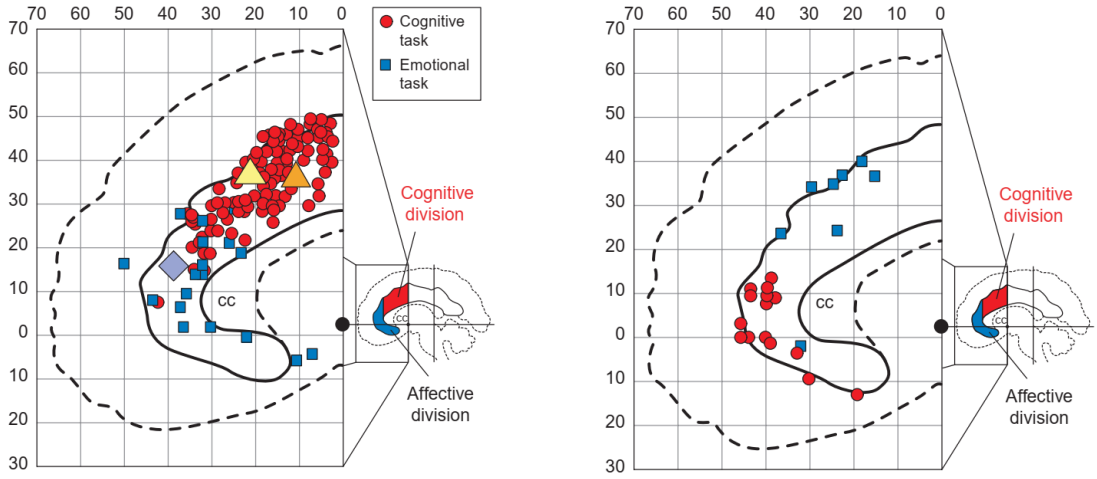


Figure 1. Functional divisions of the ACC based on a meta-analysis of Activations and Deactivations during cognitive and emotional studies.

Activations (A) and deactivations (B) are shown in 2-D spatial coordinates. The cognitive division is activated by Stroop and Stroop-like tasks divided attention tasks, and complex response selection tasks. It is deactivated (i.e. shows reduced blood flow or MR signal) by emotional tasks. The affective division is activated by tasks that relate to affective or emotional content, or symptom provocation. It is deactivated by cognitively demanding tasks. A direct comparison within the same subjects supports the cognitive versus affective distinction. The orange triangle indicates the activation of the cognitive division during the cognitive Counting Stroop (Bush et al., 1998). The same group of subjects activated the affective division (blue diamond) while performing the Emotional Counting Stroop (Whalen et al., 1998). Although matched normal controls activated the cognitive division during the Counting Stroop (yellow triangle), subjects with attention-deficit/hyperactivity disorder failed to activate the region (Bush et al., 1999). Abbreviation: CC, corpus callosum. Reprinted, with permission from (Bush et al., 2000). Copyright (2000) by Elsevier.

The dACC (cold cognitive ACC) (Bush et al., 2000), also known as caudal/posterior and midcingulate (Vogt, 2009) structure (Brodmann Area (BA) 24', BA 32') (Pizzagalli et al., 2006) has extensive connectivity with the dorsolateral prefrontal cortex (DLPFC), parietal cortex, premotor and supplementary motor area (Margulies et al., 2007; Niendam et al., 2012; Sander and Scherer, 2009; Spreng et al., 2013; Vincent et al., 2008; Yu et al., 2011). The rvACC (hot affective ACC) (Bush et al., 2000), also known as pregenual - subgenual structure

(Vogt, 2009) (BA 24, BA 25, BA 32) (Pizzagalli et al., 2006) is connected to regions associated with emotional processing such as the amygdala, orbitofrontal cortex, nucleus accumbens and anterior insula (Etkin et al., 2011; Greicius et al., 2003; Ma et al., 2010; Margulies et al., 2007; Sander and Scherer, 2009; Yu et al., 2011). From one perspective, literature (Bush et al., 2000; Kanske and Kotz, 2011b; Mohanty et al., 2007) observe dACC activation during cognitive tasks and rvACC activation during affective tasks.

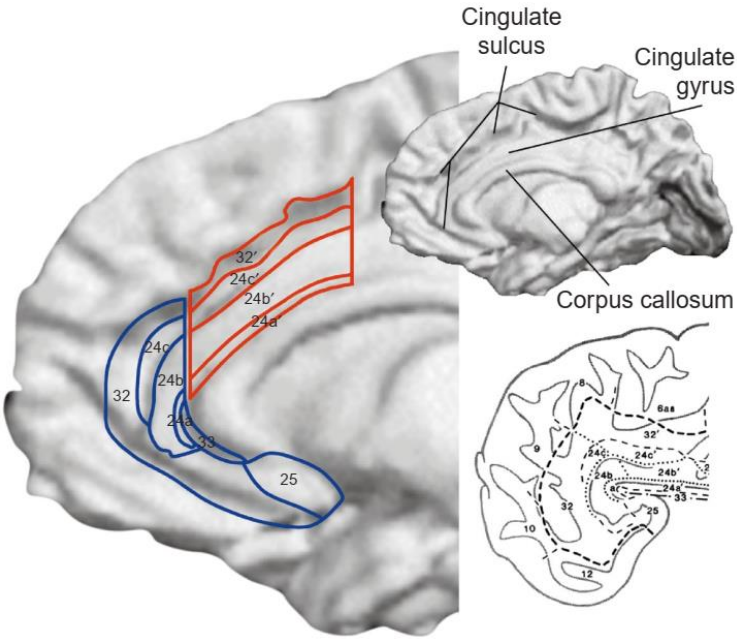


Figure 2. Anterior Cingulate Cortex Anatomy

The upper right part of the figure contains a reconstructed MRI of the medial surface of the right hemisphere of a single human brain (anterior towards the left, posterior towards the right). The cortical surface has been 'partially inflated' to allow simultaneous viewing of gyri and sulci. In this example, a single cingulate gyrus lies between the cingulate sulcus and the corpus callosum. A schematic representation of cytoarchitectural areas (numbered) of ACC is shown on the enlarged section (left). Cognitive division areas are outlined in red and affective division areas are outlined in blue. These simplified localizations are only approximations for illustrative purposes. A schematized flat map of actual anterior cingulate cortical areas is shown in the bottom right panel. The borders of each sulcus appear as thin unbroken black lines, whereas a combination of broken and dotted lines outline cingulate areas. (reprinted, with permission from (Bush et al., 2000), adapted from (Vogt et al., 1995)). Copyright (2000) by Elsevier

On the other hand, there are studies (Fuchs et al., 1985; Goldstein et al., 2005; Heckers and Konradi, 2002; Kanbara and Fukunaga, 2016; Kober et al., 2008; Östlund et al., 2003) indicating that the dACC, amygdala and hippocampus are part of a network system within the hypothalamic-pituitary-adrenal (HPA) axis that regulates emotional arousal. The dACC is also linked to autonomic cardiovascular arousal during cognitive control (Critchley et al., 2003), emotional conflict evaluation (Etkin et al., 2006, 2011), generating fear responses (Etkin et al., 2011; Mechias et al., 2010; Milad et al., 2007), viewing high-arousing pictures in women with higher emotional awareness (McRae et al., 2008) as well as with the experience of physical (Botvinick et al., 2005; Ploghaus et al., 1999) and emotional pain (Botvinick et al., 2005; Rainville et al., 1997). In (Paus, 2001), because of the extensive connections of the dACC with midline thalamus and brainstem nuclei, it was suggested that the dACC activity is modulated by the arousal state of a human being.

Meanwhile, apart from being involved in the modulation of emotional valence (Lepping et al., 2016; Rigney et al., 2018), the rvACC is also found to be activated during cognitive processes such as cognitive control regulation (di Pellegrino et al., 2007), the emotional valence modulation of cognitive processes (Shafritz et al., 2006) and emotional conflict resolution (Etkin et al., 2006, 2011). Hence, in contrast to the cold cognitive and hot affective parcellation view, the dACC is also involved in emotional tasks and the rvACC involved in cognitive tasks. Further, the dACC is found to be associated with emotional arousal and the rvACC with emotional valence.

The bidirectional signal communication and significant connectivity between the ACC and the brainstem might provide exceptional opportunities for emotion-cognition interactions (Bianciardi et al., 2016; Liddell et al., 2005; Paus, 2001; Pessoa, 2013). In support to these findings, the arguments in (Gray, 2004; Pessoa, 2014; Storbeck and Clore, 2007) indicate that

emotion and cognitive processes are mutually dependent and integrated in the brain. From our perspective, the analysis of the time courses of dACC and rvACC activity during valence and arousal modulation may provide further evidence of the mutual dependency of emotional and cognitive processes in the brain.

1.1.2 The Stroop Experiment

The Stroop Task, first developed in 1935 (Stroop, 1935) has been consistent in producing behavioral and psychophysiological Stroop effects. The behavioral Stroop effect is described as longer response time in the incongruent compared to congruent stimuli (Badzakova-Trajkov et al., 2009; Hanslmayr et al., 2008; Holmes and Pizzagalli, 2008; Koga et al., 2011; Liotti et al., 2000; Markela-Lerenc et al., 2004; Ortiz-Terán et al., 2013; Silton et al., 2010; Tillman and Wiens, 2011). In the original Stroop task, participants took an average of 47s longer naming the colors of words printed in incongruent ink colors than naming the colors of solid color square. Throughout the years, many modifications have been made to the original Stroop experiment, including spatially separating color and word in the experiment (Kahneman and Chajczyk, 1983). Despite this, the Stroop effect is found to be still intact.

On the realm of the interplay between emotion and cognitive processes, publications (Cromheeke and Mueller, 2014; Mueller, 2011) have surprisingly reported experimental studies from the classical emotional Stroop task (Gotlib and McCann, 1984). The emotional Stroop effect, defined as longer RT in naming the color of emotional words in comparison to neutral words (Chajut et al., 2010a; Dalgleish, 2008; Williams et al., 1996) measures attention bias to emotional words (Eide and Kemp, 2002; Gotlib and McCann, 1984). In 2010, a variation of the emotional Stroop task (Chajut et al., 2010b) was developed in combination of elements in (Kahneman and Chajczyk, 1983) to measure cognitive control in the presence of an

emotional context. The modified emotional Stroop effect is described as the difference of RT between incongruent and congruent stimuli. The experiment successfully imported the cognitive domain of the Stroop effect into the affective domain of the emotional Stroop.

Stroop-based EEG experimental studies have localized the prominent N200 (Silton et al., 2010), N450 (Hanslmayr et al., 2008; Liotti et al., 2000; Markela-Lerenc et al., 2004) and late negativity (Hanslmayr et al., 2008; Holmes and Pizzagalli, 2008; Silton et al., 2010) Stroop-sensitive ERP markers at the ACC. The earlier N200 component, a negative fronto-central deflection in the range of 140 to 340 ms post-stimulus has been reported in Stroop studies such as (Holmes and Pizzagalli, 2008; Ortiz-Terán et al., 2013; Silton et al., 2010). The N450 negative deflection ranging from 350 to 550 ms and the late negativity effect ranging from 600 to 800 ms, have also been consistently reported, with their maxima occurring over fronto-central electrodes (Badzakova-Trajkov et al., 2009; Hanslmayr et al., 2008; Holmes and Pizzagalli, 2008; Koga et al., 2011; Liotti et al., 2000; Markela-Lerenc et al., 2004; Ortiz-Terán et al., 2013; Silton et al., 2010; Tillman and Wiens, 2011). Thus, the N200, N450 and late negativity windows will be extensively studied in the emotion-cognition experiment with healthy subjects in Study 1. Significant valence and arousal modulating windows will be compared between HC and SZ subjects in Study 2.

1.1.3 Emotional Valence and Arousal

Evidence shows that emotional valence and arousal are separately associated with behavioral and physiological responses (Hempel et al., 2007; Llerena et al., 2012; Padmala et al., 2018; Vrana et al., 1988). They influence different brain regions (Anders et al., 2004; Dolcos et al., 2004; Sieger et al., 2015) at relatively separate stages (Gallant and Dyson, 2016; Gianotti et al., 2008; Olofsson et al., 2008). Past studies suggested that valence mainly

modulates early ERP components, whereas arousal mainly modulates late components in pure affective tasks. Studies using affective pictures (Carretié et al., 2004; Van Strien et al., 2009), auditory emotional prosody (Paulmann et al., 2013) and emotional words (Delaney-Busch et al., 2012; Gianotti et al., 2008) show that emotional valence is processed earlier compared to emotional arousal.

However, findings in the realm of the interplay between emotion and cognition remain unclear. Emotional valence has been found to modulate the N200 Go/No-Go ERP within the ACC (Albert et al., 2010) and the Go/No-Go fMRI within the rvACC (Shafritz et al., 2006). The P3a is suggested to be modulated by emotional valence and the P3b by arousal in an emotion-cognition oddball-like task (Delplanque et al., 2006). Emotion (without valence-arousal dissociation) modulated the emotion-cognition flanker task at the N200 window and the emotion-cognition Simon task at the N400 window within the rvACC (Kanske and Kotz, 2011b). The No-Go P3 shows differential modulation of emotional arousal in healthy controls and patients with ADHD (López-Martín et al., 2015). To the best knowledge of the author, the effects of emotional valence and arousal on the emotion-cognition Stroop task has not been investigated.

1.1.4 Patients with SZ

Remarked as the most complex emotional disorder to treat among all emotional disorders, Schizophrenia has a prevalence rate of 1% of the world population (Rodrigues-Amorim et al., 2017; Wierońska et al., 2016). Patients with Schizophrenia experience greater amplitude of emotional reactivity because of the mismatch, or breakdown between emotion and other channels in the brain (Benedetti et al., 2011); mainly observed in areas of the brain connected to cognition (Kring and Elis, 2012). Patients may also experience the absence of

emotional display because of this abnormality (Anticevic and Corlett, 2012). Schizophrenia is associated with disruption in thought, behavior and emotion. In this context, the anterior cingulate cortex (ACC) plays a prominent role, with different roles of the dACC and the rvACC.

Current research shows existing dysconnectivity between the ACC and hippocampus (Cui et al., 2015); and the dACC and amygdala (Liu et al., 2014), leading to behavioral deficits in SZ subjects (Das et al., 2007; Williams et al., 2004)**.** These are caused by increased levels of cortisol that affects the HPA axis by reducing hippocampus volume (C. Conrad, 2008; Mondelli et al., 2010), significantly reducing amygdala (Buckley, 2005) and the amygdala-hippocampal complex volume in SZ subjects (Shenton et al., 2001). The HPA axis is found to be disturbed in SZ subjects with severe negative symptoms (Kaneko et al., 1992). SZ subjects are prone to experience higher levels of cortisol and dysregulation of this stress hormone compared to HC (Bradley and Dinan, 2010; Steen et al., 2011; Walder et al., 2000; Yılmaz et al., 2007). Emotional arousal activates cortisol release in humans (Cahill and McGaugh, 1998). High levels of cortisol is also associated with increased arousal (Abercrombie et al., 2005; Dabbs and Hopper, 1990). The neural diathesis-stress model and its extended versions (Jones and Fernyhough, 2007; Nuechterlein and Dawson, 1984; Pruessner et al., 2017; Walker et al., 2008; Walker and Diforio, 1997) theorized that emotional stress might trigger psychosis in vulnerable individuals.

The rvACC is connected with the ventral striatum (Ongür and Price, 2000), nucleus accumbens (Nacc) (Ongür and Price, 2000), anterior insula (Yu et al., 2011) and orbitofrontal cortex (OBF) (Ongür and Price, 2000; Yu et al., 2011); all well-established components of the salience network. Attentional selection is determined by the salience of a stimulus and emotional valence is a determinant for salience (Niu et al., 2012). A caveat to the current SZ

literature are inconsistent findings on the relation of emotional valence with cognitive impairment and the dysfunction of the rvACC. For instance, negative valenced items are found to promote cognitive impairment in SZ subjects (Fear et al., 1996; Habel et al., 2010b; Mohanty et al., 2005). On the other hand, they had nonsignificant effects in (Herbener et al., 2007). SZ subjects demonstrated rvACC hypoactivity during errors of commission task (Laurens et al., 2003; Polli et al., 2008), related to affective dysfunction (Bates et al., 2002; Laurens et al., 2003; Polli et al., 2008). While violent SZ male subjects experience rvACC hyperactivations when viewing negative images, non-violent male SZ and HC subjects had nonsignificant rvACC activation difference (Dumais et al., 2016). (Mohanty et al., 2005) also found nonsignificant differences in the modulation of rvACC activity between schizotypy and HC subjects in the negative valence condition. The variation in these findings might be explained by factoring in the two dimensional valence and arousal elements in experimental paradigms.

This dissertation comprises of two EEG experiments conducted to ascertain the influences of emotional valence and arousal on cognitive control in healthy subjects (Study 1); and to compare behavioral responses and temporal dynamics of the modulations of emotional valence and arousal on cognitive control in healthy controls (HC) and patients with Schizophrenia (SZ) (Study 2) using a modified emotional Stroop task.

1.2 Problem Statement

The complex interplay of emotional and cognitive processes is present in our daily lives. Unbalanced emotion-cognition interaction might be destructive, such as those observed in anxiety and mood disorders. The emergence of world issues such as mass violence, terrorist attacks, religious, racial or ethnic hatred and discrimination, natural disasters and tragedies,

accompanied by modernization, lifestyle and stressful life events contribute to the prevalence of mental health disorders (Krabbendam, 2005; Miller and Rasmussen, 2010; Murthy and Lakshminarayana, 2006; Park et al., 2015; Steel et al., 2009). Moreover, patients suffering from psychiatric disorders struggle to remain balanced under the influences of extreme emotions and stressors (Brown et al., 2002; Kuipers et al., 2006; Olff et al., 2005). Thus, unveiling and understanding the neurobiology and neuropsychiatry aspects of emotion-cognition interaction is critical as the aggravation of the dysfunctional emotion-cognition interactions in patients with psychiatric disorders is disastrous and debilitating. Although a remarkable acceleration of research focused on the interplay of emotion and cognition have emerged, none have yet to explore the temporal dynamics of the impact of emotional valence and arousal on cognition.

Several publications (Cromheeke and Mueller, 2014; Mueller, 2011) report the classical emotional Stroop effect in the realm of emotion-cognition. The emotional Stroop task, however, measures attention bias to emotional words (emotional domain) and not cognitive interference (cognitive domain). In the most recent development, an emotion-cognition Stroop task (Chajut et al., 2010b) has been developed to investigate the influence of emotion on cognitive control. To the best of our knowledge, only behavioral responses have been obtained in the study. Moreover, comparisons were only made in the negative and neutral conditions. It is necessary to investigate behavioral and brain responses of the cognitive-emotional Stroop effect in all valence and arousal domains to address the limitations of previous research.

In Section 1.1.3, the inconsistencies of the time windows of the modulations of emotional valence and arousal during cognition in emotion-cognition studies were discussed, although literature on pure emotional studies show the modulation of emotional valence at an earlier ERP time window compared to the modulation of emotional arousal. To address the conflict, the investigation of the behavioral, ERP and the time course of the dACC and rvACC

activity in emotion-cognition Stroop task is crucial. Past studies have yet to achieve a functional profile with respect to emotional valence and arousal modulation in emotion-cognition tasks in healthy subjects. This is important in order to provide a standard comparison in patient or clinical studies.

Cognitive dysfunction is a core feature of schizophrenia. Cognitive deficits in patients with SZ has previously received abundant attention, as it is associated with their functional outcome (Bowie and Harvey, 2006; Soria et al., 2018). However, antipsychotic medication (Carpenter and Koenig, 2008; Feifel et al., 2016; Hill et al., 2010) and cognitive enhancement therapy (Fakra et al., 2015) typically have minimal impact towards the functional outcome of patients with SZ. Research show pure cognitive processes, such as those evaluated and trained in lots of programs may be distant from real-world applicability (Wykes et al., 2011), as the latter is largely based on socio-affective processes (Keshavan et al., 2014). Consequently, research of the interface of cognition and emotion in patients with SZ, has emerged.

Patients with SZ do not have the capacity to handle highly charged emotional-cognitive situations (Myin-Germeys et al., 2005; Watson, 2015). The dysregulation of emotional arousal within the dACC has been linked to cognitive deficits and negative symptoms in SZ subjects, however, the time window of this crucial state has not been determined. Moreover, the impact of emotional valence in modulating cognition and the rvACC activity in SZ subjects remains unclear. To address the requirements of the current state of knowledge in SZ investigation, the time course of the comparisons between the activation of the dACC and rvACC between HC and SZ subjects needs to be investigated. Abnormal emotion-cognition interactions might be critically involved in the pathophysiology of SZ.

1.3 Significance of the Study

1.3.1 Study 1

The investigation of the mechanisms of emotions mediating conflict play an important role in the ever-changing reality. The selection of appropriate responses in conflicting situations is essential for surviving and thriving in the modern world. Central to the components in the brain mediating cognitive and emotional processes are the dACC and rvACC. Research on the complex nature of the integration between emotional and cognitive processes within the ACC subdivisions (Okon-Singer et al., 2015; Pessoa, 2008; Salzman and Fusi, 2010) is becoming increasingly important and crucial to be understood. This study contributes to this growing area of research by revealing the influence of emotional valence and arousal on cognitive control within the dACC and rvACC.

The sLORETA time course provides excellent temporal resolution for source activity on a millisecond by millisecond basis. It provides an excellent opportunity to define electrophysiological processes temporally, in contrast to other neuroimaging technology such as fMRI and PET. The understanding of the time course of the activation within the ACC subdivisions during emotion-cognition interaction enables one to generate more sophisticated premises, assumptions, speculations and predictions about emotion-cognition experiences. For example, thus far it is unknown whether the activation in the rvACC or dACC occurs earlier or later within the sequence of emotion-cognition processes. If these activations occur earlier, one might argue for more automatic processes driving the modulations of emotions on cognition. However, if these activations occur later, they may support top-down processes controlling response selection.

The time course further illustrates the dynamics within the dACC and rvACC which is pivotal for understanding the effect of emotional valence and arousal during cognitive control. This provides the opportunity of detecting any valence-conflict or arousal-conflict effects within specified regions. This study examines the temporal dynamics of the effects of emotional valence and arousal on cognition, which, to the best of our knowledge, has not been addressed previously. Furthermore, current literature has identified several brain regions involved in the generation of induced emotional valence and arousal, but there is no information available about the temporal dynamics and the intensity of activation within the classified regions.

Behavioral performance is closely linked to the modulation of cortical evoked activity providing explanations of underlying brain-behavior integration. The current study addresses this aspect, which have not been previously explored in the emotion-cognition Stroop experiment. Further, the attainment of the time window of the dACC and rvACC activation in the emotion-cognition Stroop task in healthy subjects serves as a benchmark for future patient studies.

1.3.2 Study 2

Evidence suggest that SZ is a severe condition affecting several different domains including cognitive and emotional processing. In this context, the ACC plays a prominent role, with different but interrelated roles of the dACC and rvACC. This study would address the urgent need of understanding emotion-cognition interactions in patients with SZ through the investigation of the time course within the dACC and rvACC in an emotion-cognition Stroop experiment.

Currently, very few studies are focused on investigating arousal-conflict or valence-conflict related deficiencies in SZ subjects. Evidence relates SZ subjects with arousal dysregulation within the dACC, associated with cognitive impairment, however, the time window of this crucial state has not been determined. Moreover, literature is inconsistent on the relation of emotional valence with cognitive impairment and the dysfunction of the rvACC. This research addresses the gaps and conflicts of previous studies by investigating the impact of emotional valence and arousal on cognitive control within the dACC and rvACC in patients with SZ, which may lead to the discovery of the brain regions involved in aberrant emotion-cognition modulations. It is hoped that the findings of the dissertation would spark a boost within emotion-cognition research in SZ, leading to improved intervention strategies. A breakthrough in this area could possibly result in an increase in the quality of life of patients suffering from SZ, leading to societal wellbeing.

1.4 Rationale for the experiments

Recent years have witnessed not only the emergence new findings, but also challenges to old ideas in the field of emotion-cognition. There remains an open question as to how emotional valence and arousal influence cognitive control and how does it affect the brain? What are the implications of these findings towards patients with psychiatric disorders? Patients with SZ for example, have been associated with arousal and valence related cognitive deficiencies.

One method of investigating the area of emotion-cognition interrelations is by examining how emotions modulate cognition (Storbeck and Clore, 2007). The focus of previous (ERP and fMRI) studies investigating cognitive-emotional interactions were not on the valence and arousal dimensional effect. This issue was addressed with a ROI (dACC and rvACC) time course study on the impact of emotional valence and arousal on cognitive control.

The time course analysis illustrates the dynamics within the dACC and rvACC which is pivotal for understanding the effect of emotional valence and arousal during cognitive control.

An existing emotion-cognition Stroop behavioral study in the realm of ERP and ROI current density was employed. The experiment was then performed on SZ subjects. The parameters of the study were the RT, the N200, N450 and late negativity ERP windows and the time course of the dACC and rvACC activity.

1.5 Research objectives

1.5.1 Study 1

1) To examine the time course of the current density within the dACC and rvACC in an emotion-cognition Stroop Task

2) To determine the time window and the brain region responsible for modulating valence during conflict

3) To the determine the time window and brain region responsible for the modulation of arousal during conflict.

1.5.2 Study 2

1) To compare the time courses of the current density within the dACC and rvACC between SZ subjects and HC subjects in an emotion-cognition Stroop Task.

2) To determine the time window and brain region responsible for the existence of aberrant arousal-conflict modulation in SZ subjects.

3) To determine the time window and brain region responsible for the existence of aberrant valence-conflict modulation in SZ subjects.

1.6 Research Scope

In the present dissertation, we examined the modulations of emotional valence and arousal on each of the Stroop ERP markers: the N200, N450 and late negativity in healthy subjects; and the N450 and late negativity as a comparison between HC and patients with SZ. The investigation of the RT, ERPs and sLORETA ROI source activity during conflict in various levels of emotional valence (neutral, positive, negative) and arousal (low, high) is necessary as it would unravel possible valence and arousal modulations at specific Stroop-sensitive time windows.

The sLORETA ROI source localization analysis elucidates the time course of the dACC and rvACC activation during the emotional Stroop task. This might result in achieving a functional profile (within our ROIs: the dACC and rvACC) with respect to the influence of emotional valence and arousal in modulating cognitive control. The RT, ERP, sLORETA ROI parameters will be compared between HC and patients with SZ. Although whole brain analysis and connectivity analysis of other sub-regions of the ACC and other emotional-cognitive regions of the brain are excellent methods of investigating emotion-cognition brain interactions, they will not be discussed in this dissertation as these methods are beyond the scope of the dissertation.

1.7 Hypotheses

1.7.1 Study 1

The central hypotheses of Study 1 were: i) valence modulates the early ERP Stroop marker within the rvACC and ii) arousal modulates the late ERP Stroop effect within the dACC in healthy subjects.

On the basis of previous findings discussed in Sections 1.1.1 and 1.1.3, emotional valence is expected to modulate an earlier ERP Stroop marker within the rvACC and emotional arousal is expected to modulate a later ERP Stroop window within the dACC.

1.7.2 Study 2

In Study 1 (Feroz et al., 2017), it was observed that emotional arousal modulated the dACC activity during late negativity where emotional arousal likely initiated response conflict resolution. Evidence from the literature (discussed in Section 1.1.4) relates SZ subjects with arousal dysregulation within the dACC, which is associated with cognitive impairment. Thus, SZ subjects were hypothesized to show deficits in modulating dACC activity at the late negativity window, interfering with conflict resolution in the high arousal condition.

Meanwhile, Study 1 also found that in healthy subjects, emotional valence modulated the rvACC activity at the N450 window, reflecting initial selective attention towards emotional word valence. Inconsistent findings on the relation of emotional valence with cognitive impairment and the dysfunction of the rvACC in patients with SZ provides a basis for our next hypothesis. Deficits in the modulation of emotional valence within the rvACC at the N450 window in SZ subjects was hypothesized. Furthermore, existing peak and time differences in the time course activity between SZ and HC subjects were also hypothesized.

2 Material and Methods

Because the methodological parameters for EEG recordings, data pre-processing and statistical analysis are largely identical for both Study 1 and Study 2, they will be described conjointly in Sections 2.1, 2.4, 2.5, 2.6, 2.7, 2.8 and 2.9 (except 2.9.3.1 and 2.9.3.2). Various different methods have been utilised to investigate emotion-cognition interactions in the brain. A major advantage of EEG, compared to other technologies such as fMRI and PET is the excellent temporal resolution (Aine, 1995; Mulert et al., 2004). Hence, it is one of the most well-known tool for assessing the temporal dynamics of brain activity. The central methods applied in EEG data analysis in this dissertation are the ERP and the sLORETA ROI current density analysis.

2.1 Ethics Statement

Prior to commencing both Study 1 and Study 2, ethical clearance was sought from the Ethics Committee of the Medical Association Hamburg. The protocols were carried out in accordance with the seventh revision of the Declaration of Helsinki (2013). Written informed consent from all participants were obtained after an explanation of the objective of the study and the nature of the experimental procedures were provided. It is ensured that all participants understood that they were allowed to discontinue their participation at any time during the experiment.

2.2 Sample description

2.2.1 Study 1: Healthy participants

Twenty-seven healthy subjects (sixteen females; aged 20-56 years; mean ± standard deviation, 29.15 ± 8.45 years) enrolled in this study. They were recruited randomly via the internet and word-of-mouth from Hamburg and its surrounding area. Only right handed participants were included in the study. Handedness was assessed with the German version of Edinburgh Handedness Manual (Oldfield, 1971)**.** All participants were native speakers of the German language and had normal to corrected-to-normal vision. Participants with a history of neurological, psychiatric or major medical disorders, color blindness and a history of reading disorder were excluded from this study.

2.2.2 Study 2: Patients with Schizophrenia and matched healthy controls

Twenty patients with SZ and twenty HC participated in this experiment. Patients who met the DSM-IV criteria for SZ were recruited through the Psychosis Center of the Department of Psychiatry of the University Medical Center Hamburg-Eppendorf. HC subjects were recruited via the internet and word-of-mouth from Hamburg and its surrounding area.

Exclusion criteria for both participants were current substance abuse or dependence, the presence of major somatic or neurological disorders, color blindness and a history of reading disorder. For HC subjects, additional exclusion criteria were any previous psychiatric disorder or treatment. All participants were native speakers of the German language and had normal to corrected-to-normal vision. The presence of inclusion and exclusion criteria in patients was assessed by a clinical psychiatrist or psychiatric trainee. Handedness was assessed with the German version of the Edinburgh Handedness Manual (Oldfield, 1971).

2.3 Positive and Negative Syndrome Scale (PANSS)

The Positive and Negative Syndrome Scale (PANSS; (Kay SR, Fiszbein A, 1987)) was used to assess the severity of clinical symptomatology in patients with Schizophrenia in Study 2. The subscores for positive, negative, disorganization, excitement and distress symptoms were created according to a five factor model of the PANSS (van der Gaag et al., 2006). Based on reported trajectories of antipsychotic treatment response (Case et al., 2011; Stauffer et al., 2011), clinical severity ratings were used for analyses only if they were separated from EEG analyses by no more than a week. Thus, appropriate clinical ratings were available for 18 patients.

During EEG recording, nine SZ patients were in treatment with atypical antipsychotics and two with typical antipsychotics. Furthermore, four patients were in treatment with antidepressants and one under treatment with mood stabilizer. Ten patients were not under any psychotropic medication. No subjects received benzodiazepines or anticholinergic agents. The groups were matched with respect to age, sex, and educational level. Demographic characteristics of the groups, and clinical characteristics of SZ participants are presented on Table 1.

Table 1. Participant Demographic and Clinical Characteristics

	Healthy Controls		Schizophrenia Patients		T/χ^2	p
	***N* or Mean**	**SD**	***N* or Mean**	**SD**		
Gender (m/f)	14/6		14/6		0.00	1.00
Age	32.00	9.38	32.65	9.78	0.21	0.83
Level of Education	2.65	0.49	2.35	0.75	0.69	0.71
Handedness (R/L)	19/1		18/2		1.05	0.30
Medication dose Chlorpromazine equivalent (mg/day)			232.5	325.36		-
Five-Factor PANSS Scores						
Positive symptoms			11.39	6.17		-
Negative symptoms			12.28	6.52		-
Disorganization			12.33	4		-
Excitement			9.56	2.23		-

Emotional distress	11.83	4.02	-
TOTAL PANSS	**42.44**	**11.04**	-

2.4 Experimental Paradigm

The modified emotional Stroop paradigm was adapted from a previous behavioral study (Chajut et al., 2010b). Stimuli consisted of an emotional word and a color word, horizontally aligned, appearing to the left and right of a fixation point (see Figure 3). The emotional words were presented in either red, green, blue or yellow color. Color words were either congruent or incongruent to the color of the emotional word. The color words, "rot", "grun", "blau" or "gelb" were always printed in white and were the German words representing red, green, blue and yellow.

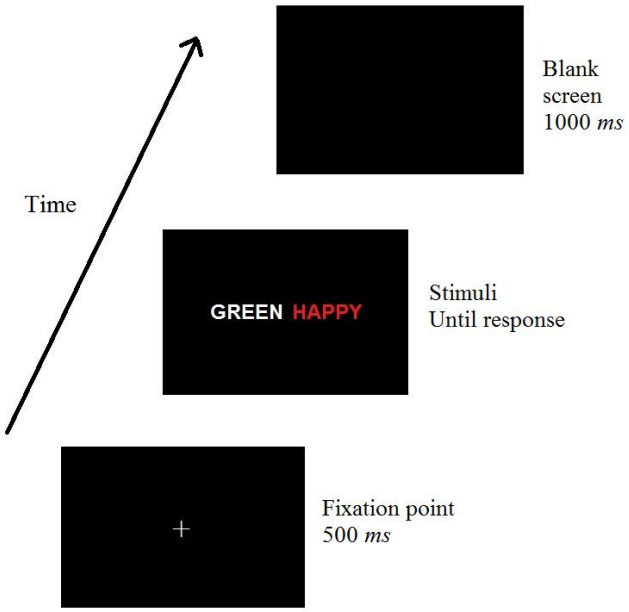


Figure 3. A schematic illustration of the emotional Stroop paradigm, adapted from (Chajut et al., 2010b).

Emotional words were selected from two large databases of emotional ratings (with respect to the valence and arousal levels) of German words. A total of fifty two emotional words were selected from Leipzig Affective Norms for German (LANG) (Kanske and Kotz, 2010, 2011c) and forty four words were selected from Berlin Affective Word List Reloaded (BAWL-R) (Võ et al., 2009). Words in LANG are rated (with regard to valence and arousal) using a nine-point Likert scale while in BAWL-R, valence is rated on a seven-point scale and arousal on a five-point scale. Selected words were categorized into 3 different valence classes (neutral, positive and negative) and 2 different arousal classes (high and low) based on their normative ratings in these databases.

Prior to word selection, using linear transformation, the valence and arousal ratings of the words from BAWL-R were transformed to a nine-point scale, similar to the words from LANG. These ratings were then analyzed using a 2 × 2 factorial analysis of variance (ANOVA) (valence × arousal). The test revealed a significant main effect of valence [$F(4,178) = 168.57$, partial $\eta^2 = 0.7911$, $p < .01$]. Bonferroni-*t* post-hoc tests revealed that positive words were more pleasant than neutral ($t(62) = 16.3894$, $p < .01$) and negative words ($t(62) = 25.5331$, $p < .01$) while negative words were more unpleasant than neutral words ($t(62) = -17.1540$, $p < .01$). Arousal ratings were significantly higher for high arousal compared to low arousal words [$F(2,89) = 205.059$, partial $\eta^2 = 0.8217$].

Literature (Ashley and Swick, 2009; Holle and Neely, 1997; McKenna and Sharma, 2004) shows that attentional capture in relation to the emotional Stroop effect is found in behavioral studies that used the blocking method, but not in those using the randomly intermixed method. The decision to use the blocking method was based on this consideration and previous emotional Stroop fMRI (Herrington et al., 2005; Mohanty et al., 2007; Whalen et

al., 1998) and EEG (Cacioppo et al., 2015; Stewart et al., 2011; van Hooff et al., 2008) studies that implemented this technique. Six blocks of stimulus presentation were constructed, namely low-arousal neutral, high-arousal neutral, low-arousal positive, high-arousal positive, low-arousal negative and high-arousal negative. The order of the appearance of all six blocks was randomized across participants, where both (high and low) arousal blocks of each valence class appeared consequently. For example, the fifth participant was assigned to a block arrangement of high-arousal negative, low-arousal negative, high-arousal neutral, low-arousal neutral, high-arousal positive and low-arousal positive.

Each block contained 16 emotional words, in two groups of 8 where each word group was allocated two different colors. Thus, in each block there were (2 x [2 (colors) x 2 (congruence) x 2 (positions) x 8 (words)]) = 128 different stimuli, which were presented in a pseudo-random order with the condition that no colour appeared twice in succession. The stimuli were generated by a Pentium (R) Dual Care CPU, Dell Optiplex 780 computer, displayed on Tay Tech Plug and Play monitor (screen resolution 1280 × 1024, refresh rate 60 Hz). The gap between the two horizontal stimulus words (Arial font, size 28) was 5 pixels, presented in black background.

2.5 Task and Procedure

Prior to the actual task, a color-to-key acquisition session and a practice session were conducted for all participants. The color-to-key session was designed to help participants rehearse and memorize the color mapping of the buttons on the response keypad. In this session, four squares were featured on-screen, two on the left and two on the right hand side. During each trial, one square was filled with a color that was mapped to the keypad. Participants executed the task bimanually, using the index and middle finger of the right hand for the colors yellow and blue, respectively, and the middle and index finger of their left hand for the colors

red and green, respectively. This session consisted of 84 trials in a single block with each color appearing 21 times.

After the color-to-key acquisition session, participants were given a practice session with 41 trials that were not presented during the actual task. In the practice session and the experimental task, each trial started with a fixation cross shown at the center of the screen for a duration of 500 *ms*. Then, a stimulus was presented and remained on screen until the participant initiated a response by pressing the button of the corresponding color on the keypad (Chajut et al., 2010b; Schroeter et al., 2002). Following the response, the screen went blank for 1000 *ms*, before the next trial started with a fixation point. Participants were instructed to always keep their eyes fixated on the monitor and fingers resting on the appropriate keypad buttons during the task. On completion of each block, a minimum of three minutes rest period was allocated to reduce emotional lingering effects (Sharma and McKenna, 2001).

2.6 EEG Recording

EEG recordings took place in a sound-attenuated and electrically shielded room. Participants were seated on a slightly reclined chair facing a 19" computer monitor in a dark room. The distance between the eyes of the subjects and the monitor was approximately 1 *m*. Continuous EEG activity was recorded using Ag/AgCl electrodes mounted in a 64 channel actiCAP system (Brain Products, Munich, Germany). Electrodes were positioned in an extended 10/20 system with the additional positions: AF7, AF3, AF4, AF8, F5, F1, F2, F6, F10, FT9, FT7, FC3, FC4, FT8, FT10, C5, C1, C2, C6, TP7, CPz, TP8, P5, P1, P2, P6, PO3, POz, PO4. Eye movements were recorded by two horizontal EOG channels positioned at the outer canthi of the left and right eye and two vertical EOG channels, one below (infraorbital) and one above (supraorbital) the right eye. All electrodes were referenced during recording to

FCz. Electrode AFz served as ground. Data were collected at a rate of 1000 Hz. The impedances were kept below $5k\Omega$ for all recordings.

2.7 Software

Stimulus presentation and the recording of behavioral data was done with Presentation Version 16.3 (Neurobehavioral Systems). The EEG recording was acquired using the Brain Vision recorder software version 1.20 (Brain products, Munich, Germany). EEG preprocessing and ERP analysis was done with the Brain Vision Analyzer (BVA) software version 2.0 (Brain products, Munich, Germany). Following that, ROI source localization analysis was conducted with the LORETA KEY software package (software update 2008-November-04) as provided by the KEY Institute for Brain-Mind Research University Hospital Psychiatry, Zurich at http://www.uzh.ch/keyinst/LORETAOldy.htm. Finally, statistical analyses of behavioral, questionnaire and EEG data were conducted using STATISTICA 8.0, SPSS version 20 and MATLAB R2013b.

2.8 EEG Preprocessing

EEG data were band pass filtered (0.3 – 30 Hz) and down-sampled to 250 Hz. Upon automatic detection (amplitude criterion of ± 80 µV) and verification by visual inspection, intervals containing movements and muscle artifacts in any EEG channel were excluded from further analysis. Eye movements and blinks were then corrected with ICA. After re-referencing to common average reference, epochs of 1700 ms (200 ms pre to 1500 ms post-stimulus) were created for each condition and were evaluated for the ERP Analysis. Finally, we performed a baseline correction with a period of 150 ms before stimulus.

2.9 Statistical Analysis

Following the rationale described in Section 1.4 of the dissertation, the assessment of the hypothesis regarding the time windows and brain regions involved in the modulation of emotional valence and arousal on cognition in healthy subjects and patients with SZ was conducted using behavioral measures and EEG signal. After participants performed the modified emotional Stroop (Chajut et al., 2010b) experiment, RT, event related potentials (ERP) and sLORETA ROI time course data were analyzed offline.

In compliance to the sphericity requirement of the repeated measures ANOVA, the adjusted Greenhouse-Geisser correction to the univariate repeated measures ANOVA *p*-values, the unadjusted degrees of freedom and epsilon values were reported throughout this paper. All multiple comparison tests conducted in this study used the Bonferroni t method as it is robust to violations of sphericity (Maxwell, 1980) and can be used regardless of whether the F test is significant (Games, 1971; Hancock and Klockars, 1996; Howell, 2013; Wilcox, 1987).

2.9.1 Behavioral Data: Mean Error Rates and RT

Mean RT and error rates were computed for each subject. Trials with incorrect responses were only used in the error rate calculation and discarded from all further analyses (Chajut et al., 2010b). The mean RT and error rates were subjected to a three-way repeated measures ANOVA (with factors valence, arousal and congruence) for Study 1. In Study 2, repeated measures mixed-design ANOVA was conducted on the RT and accuracy data with stimulus type as the within-subjects factor (with factors valence (positive, neutral, negative), arousal (low, high) and congruence (congruent, incongruent)) and group (SZ, HC) as the between subjects factor.

2.9.2 Behavioral Data: Ex-Gaussian

A recommended alternative (Heathcote et al., 1991; Lacouture and Cousineau, 2008; Ratcliff, 1993) to the mean RT analysis is examining the whole RT distribution itself. The ex-Gaussian distribution, a convolution of the normal and exponential distribution (Burbeck and Luce, 1982) is one of the most useful theoretical distributions that successfully summarizes RT experimental data. The three parameters of the ex-Gaussian distribution are the mean of the normal distribution, μ, the standard deviation of the normal distribution, σ and the mean and standard deviation of the exponential distribution, τ. To find the optimal values of μ, σ and τ that best described the experimental data, the ex-Gaussian distribution was fitted to the RT data using the SIMPLEX routine written in MATLAB source code (Zandbelt, 2014). The best fitting parameter values were then selected using the maximum likelihood approach. Chi-square statistics was calculated to assess the quality of fit of the fitted ex-Gaussian distribution (Heathcote et al., 1991; Penner-Wilger et al., 2002; Rohrer and Wixted, 1994).

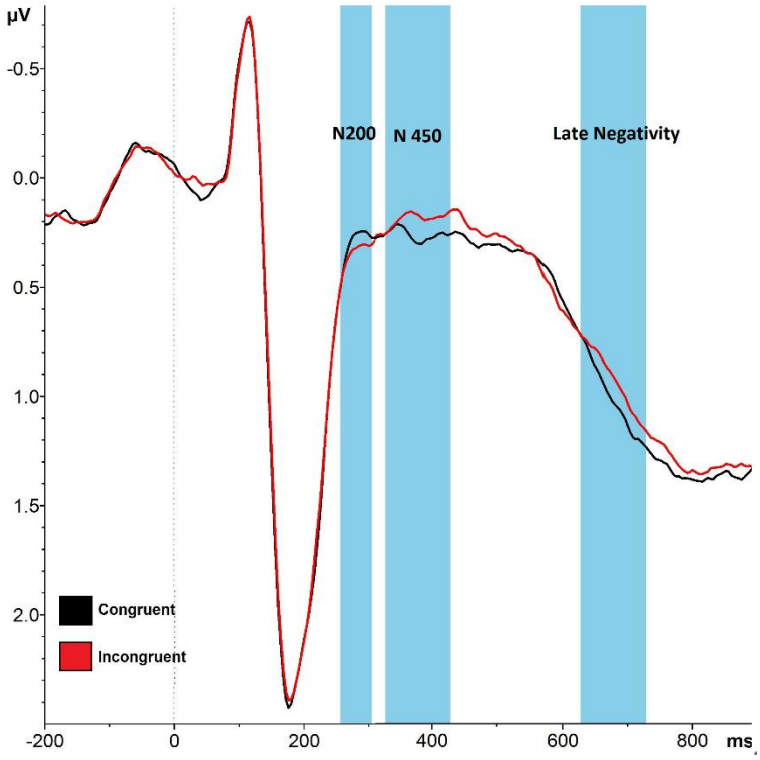
2.9.3 Event-Related Potentials

ERPs for correct response trials (after artifact removal) were averaged for each subject and condition, namely: valence (neutral, positive and negative), arousal (low and high) and congruence (congruent and incongruent). In Study 1, the number of trials per condition ranged from 41 to 64 trials. They did not differ significantly (main effects or interactions) across conditions [$F(2,52)=0.50$, GG epsilon $= 0.76$, partial $\eta^2=0.019$, $p=0.56$]. The number of trials per condition in Study 2 ranged from 40 to 64. There were no significant main difference in main effects or interactions across conditions [group effect; $F(1,38) = 2.80$, partial $\eta^2=0.07$, $p=0.10$].

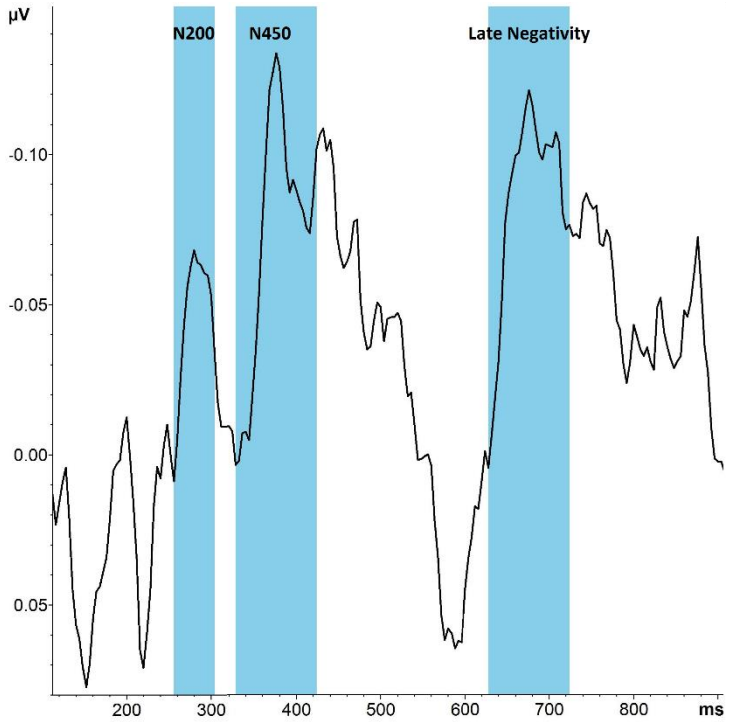
The main ERP effects of interest in both studies were the fronto-central negative deflection in incongruent compared to congruent trials across all levels of valence and arousal. The mean pooled amplitude of the fronto-central electrodes (FC5, FC1, C3, Cz, FC2, FC6 and C4, cf. (Hanslmayr et al., 2008)) was used as the dependent variable.

2.9.3.1 Study 1: Healthy Subjects

The grand-average ERP waveforms of the pooled fronto-central electrodes for the congruent and incongruent conditions (across all emotional conditions), and their contrasts (incongruent – congruent) are presented in Figure 4 (A) and (B) respectively.



(A)



(B)

Figure 4. ERP Responses.

(A) The ERP grand average wave at pooled fronto-central electrodes in the incongruent (red) and congruent (black) conditions across all emotional conditions. Time frames colored in blue are the N200 (255-305 ms), N450 (326-426 ms) and late negativity (626-726 ms) windows which were determined by the highest difference wave peak for the N200 marker ± 25 ms and N450 and late negativity marker ± 50 ms (B) The ERP grand average difference (incongruent – congruent) wave collapsed across all emotional conditions. Time windows considered for analysis are colored in blue

The N200 time window was defined as ± 25 ms from the highest peak amplitude of the grand-average difference wave and the N450 and late negativity were defined as ± 50 ms from the highest peak amplitude of the grand-average difference wave. The time windows were identified based on previous literature findings regarding the time frames of each marker. Amplitude was calculated by averaging data points within these three major time frames for color-word interference: 255 – 305 ms (N200; difference-wave peak at 280 ms), 326 – 426 ms (N450; difference-wave peak at 376 ms) and 626 – 726 ms (late negativity; difference-wave peak at 676 ms).

2.9.3.2 Study 2: A Comparison between SZ and HC subjects

Based on Study 1 (Feroz et al., 2017), the two significant Stroop time windows that modulated emotional valence and arousal during cognitive control in HC subjects were selected for congruence analysis. The N450 (326-426 ms; peak at 404 ms) and the late negativity (626-726 ms; peak at 676 ms) time frames are illustrated in Figure 5.

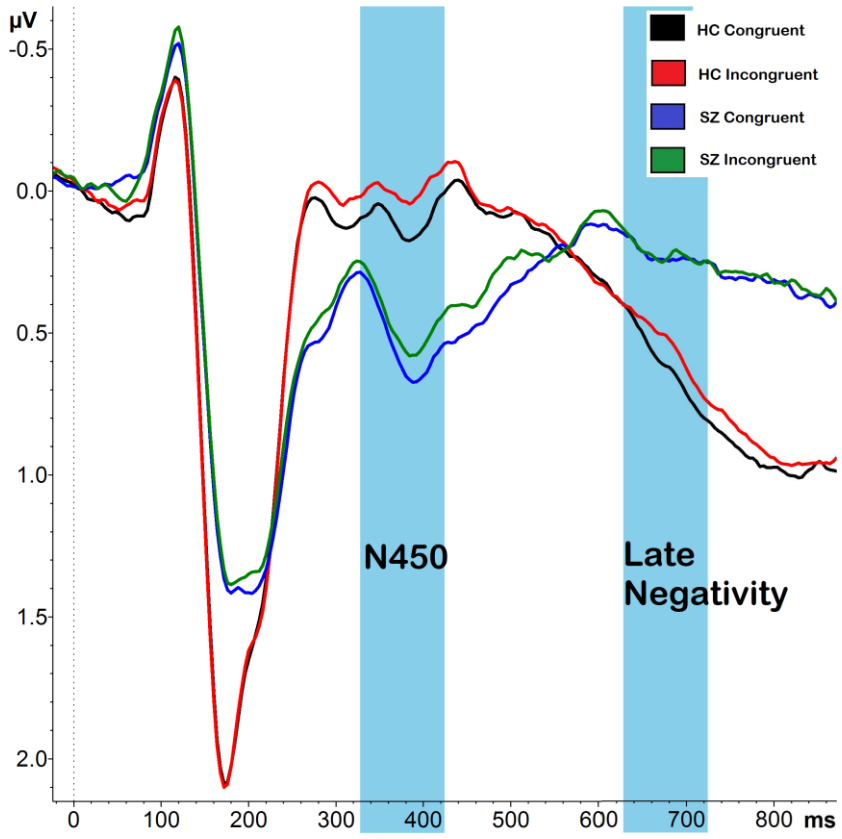


Figure 5. The ERP grand average wave at pooled fronto-central electrodes in the incongruent (red) and congruent (black) conditions for HC subjects and incongruent (green) and congruent (blue) conditions for SZ subjects across all emotional conditions.

Time frames highlighted in blue are the N450 (326-426 ms) and late negativity (626-726 ms) windows

Additionally, the P200 (139-189 ms; peak at 164 ms) and late positive component (791-841 ms; peak at 816 ms) time windows were also investigated. See Figure 6 for the ERP waveform. The P200 and late positive component windows were defined as ± 25 ms from the two highest peak amplitude of the grand-average difference wave of the HC and SZ groups.

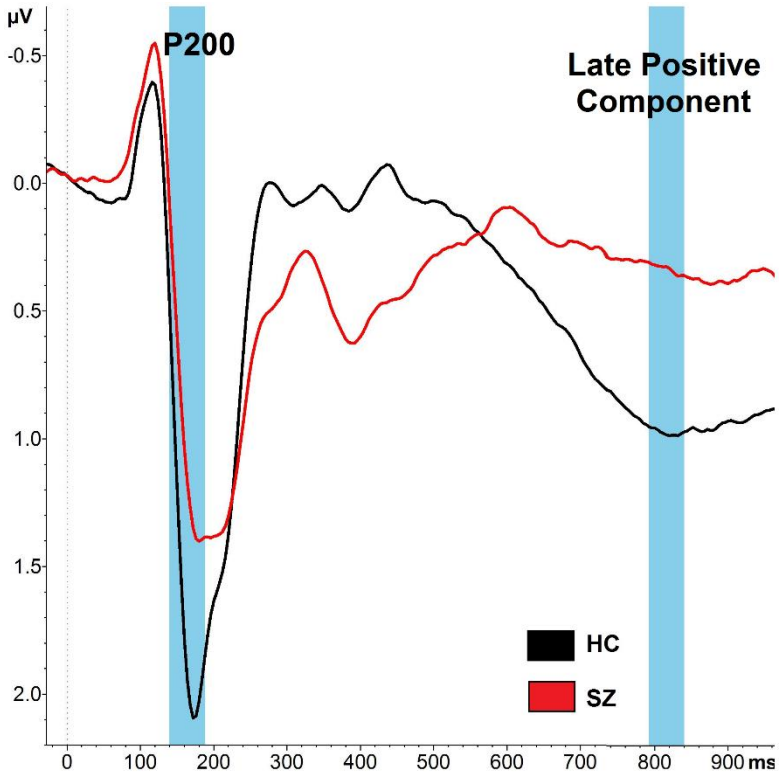


Figure 6. The ERP grand average wave at pooled fronto-central electrodes featuring the P200 and Late Positive Component windows for HC subjects (black) and SZ subjects (red).

The mean amplitudes at the pooled fronto-central electrodes at each window (N450, late negativity, P200 and late positive component), for each stimulus type (congruence, valence, arousal) were calculated and analyzed with a repeated measures mixed-design ANOVA. Valence (neutral, positive, negative), arousal (low, high) and congruence (congruent, incongruent) were defined as within-subject factors and group (SZ group and HC group) as the between-subject factor.

2.9.4 Region of Interest (ROI) Current Density

To attain the temporal course of the dACC and rvACC neural activation, the standardized low resolution brain electromagnetic tomography (sLORETA) region of interest (ROI) source localization approach was implemented. LORETA is one of the most successful techniques for source localization (Cannon, 2012; Mulert et al., 2001, 2002, 2003; Olbrich et al., 2009; Pascual-Marqui, 1999; Pascual-Marqui et al., 1994) and ROI time course representation of localized EEG activity (Mulert et al., 2004; Steinmann et al., 2014). LORETA estimates the sources underlying scalp EEG data (also known as the inverse problem) in a three-dimensional (3D) Talairach space. Its discrete, 3D distributed, linear, and weighted minimum norm inverse solution has the lowest possible localization error to test point sources (Pascual-Marqui, 2002). For each participant and condition, sLORETA solutions were computed with a realistic head model (Fuchs et al., 2002) within the source space (6239 voxels at a resolution of 5 mm) (Jurcak et al., 2007), restricted to cortical grey matter and hippocampi, as determined by the probabilistic Talairach atlas (Lancaster et al., 2000). The current density is computed as the linear, weighted sum of the scalp electrical potentials (unit in A/m^2).

Based on our hypotheses, two ROIs were selected, namely the dACC and rvACC. The definition of the ROIs was adapted from (Pizzagalli et al., 2006). The ROIs comprised of BA 32' and BA 24' for dACC and BA 32, BA 24 and BA 25 for rvACC. Using the ROI maker 3 function in sLORETA, ROIs corresponding to the two ACC subdivisions were created by including all voxels with coordinates corresponding to the respective Brodmann areas (80 voxels for each ROI) (Feroz et al., 2017). ROI voxels are illustrated in Figure 7. Following that, ERP segments (-200 to 1500 ms) were converted to sLORETA files using the EEG/ERPs to sLORETA function. Finally, the ROI current densities were computed using the sLORETA to ROI function, using the ROI definitions file previously created in ROI maker 3. Current

density values were calculated based on the average of current density values in all voxels belonging to the specific ROI at each time point. Prior to statistical analyses, in the case that the sLORETA current density data violated the normality assumption (assessed with the Kolmogorov-Smirnov test), results were transformed with natural log (ln) transformation (Miyanishi et al., 2013).

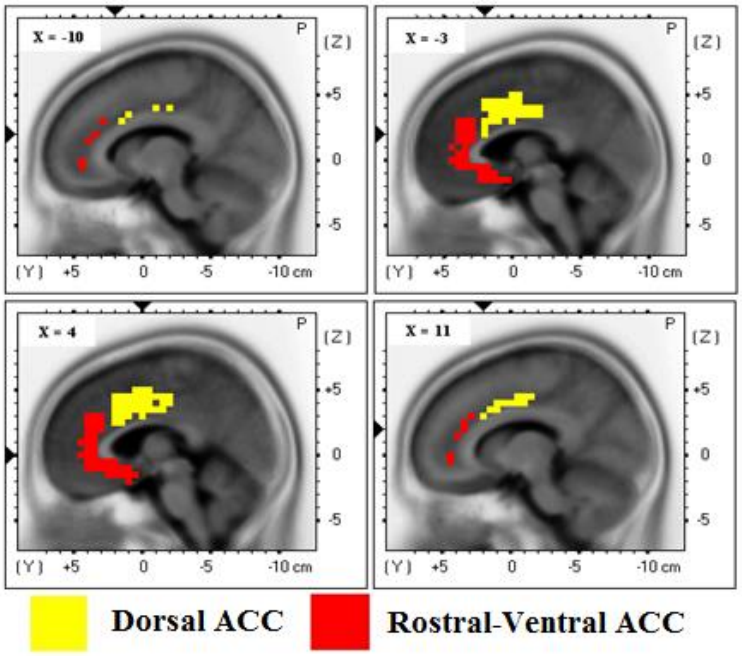


Figure 7. Regions of interest (ROI) for the current density sLORETA source localization analysis.

The position and extent of the dorsal (cognitive) (yellow) and rostral-ventral (affective) (red) ACC subdivisions were displayed on LORETA template adapted from (Pizzagalli, Peccoralo, Davidson, & Cohen, 2006). Coordinates were in mm (MNI space).

Previously, the validity of LORETA source localization solutions could only be indirectly compared with findings from similar fMRI studies. However, with the current advancements in the neuroimaging field, experimental studies combining EEG with fMRI (Mobascher et al., 2009; Mulert et al., 2004; Olbrich et al., 2009), PET (Dierks et al., 2000; Gamma et al., 2004), structural MRI (Worrell et al., 2000) and intracranial recordings (Zumsteg et al., 2006b,a) provide cross-modal validation to LORETA source localization (Pizzagalli,

2007). It has been proven in (Pizzagalli et al., 2001) that deep structures such as the ACC are correctly localized with LORETA. Further, simultaneous EEG-PET (Pizzagalli et al., 2003) study has revealed that the ACC is involved in the generation of frontal midline theta activity in humans. EEG-fMRI studies such as (Esposito et al., 2009; Juckel et al., 2012; Mulert et al., 2008, 2010) have shown the ACC as generator of ERP potentials responsible for cognitive processes.

3 Results from Experiment 1: The Influence of Emotional Valence and Arousal during Cognitive Control in Healthy Subjects

The first experiment investigated the impact of emotional valence and arousal on cognitive control, using the modified emotional Stroop paradigm. A three-way repeated measures ANOVA (with factors valence, arousal and congruence) was used to investigate RT, ERP and sLORETA ROI current density effects. In order to ascertain the relationship between RT and sLORETA ROI current density, the Pearson product moment correlation coefficient analysis was conducted.

3.1 Behavioral Data: Traditional Measures of Task Performance

3.1.1 Non-Significant Error Rate across All Conditions

The results [$F(2,52)=1.57$, GG epsilon=0.93, partial $\eta^2=0.06$, $p=0.34$] indicate no significant main effects or interactions across conditions for error rates. All analyses performed henceforth shall exclude error responses (Chajut et al., 2010b).

3.1.2 Behavioral Stroop Effect: Faster Responses in Congruent Compared to Incongruent Trials

Repeated measures ANOVA (valence × arousal × congruence) revealed a significant behavioral Stroop effect, in accordance to the hypothesis. On average, congruent trials [809.33, SE 33.15 ms] were responded to faster than incongruent trials [819.73, SE 33.21 ms] across all emotional conditions [$F(1,26) = 3.49$, GG epsilon = 1.00, partial $\eta^2 = 0.12$, $p < .05$]. These

results demonstrate conflict elicited by task. In this analysis, a one-tailed test was used due to the pre-defined hypothesis and the well-established behavioral Stroop effect in literature.

3.1.3 Valence × Arousal Interaction: Faster Responses in Low Arousal Positive Condition

A significant behavioral valence and arousal interaction effect [$F(2,52)=4.11$, GG epsilon=0.89, partial $\eta^2=0.14$, $p<.05$] was found in this study. Post hoc tests revealed significant faster mean RT in the low-arousal positive condition [750.08 ± 25.09 ms] compared to the low-arousal neutral condition [860.75 ± 49.55 ms; $p < 0.05$] and the high-arousal negative condition [861.74 ± 48.07 ms; $p < 0.05$]. A bar graph illustrating the RT valence and arousal interaction effect is presented in Figure 8. It is apparent that for the positive and negative valence items, the mean RTs were higher in the high arousal compared to the low arousal condition. In contrast, for the neutral items, the mean RT was higher in the low arousal compared to the high arousal condition.

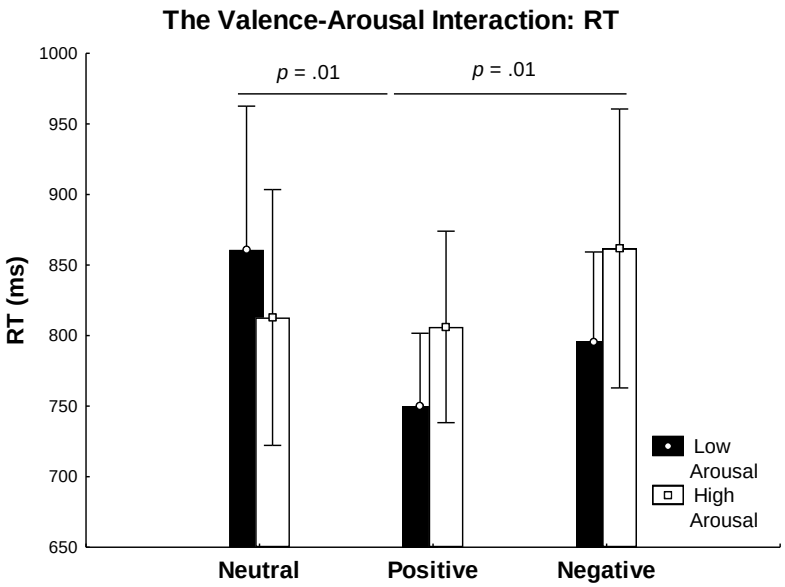


Figure 8. The Behavioral Valence-Arousal Interaction Effect.

The mean RT bar graph illustrate the significant interaction between emotional valence (positive, negative and neutral) and arousal (low and high)

3.2 Behavioral Data: The Ex-Gaussian Measures of Task Performance

3.2.1 The Ex-Gaussian μ: Higher μ in the Incongruent Condition

In this study, the ex-Gaussian analysis was conducted mainly for two reasons: 1) RT distributions are generally skewed to the right, similar to the ex-Gaussian distribution, due to extreme values (Heathcote et al., 1991; Ratcliff, 1993; Whelan, 2008). 2) Evidence (Moutsopoulou and Waszak, 2012; Parris et al., 2013; Steinhauser and Hübner, 2009) show successful isolation of different types of conflict in experimental paradigms using the ex-Gaussian method.

A three-way repeated measures ANOVA (valence × arousal × congruence) for μ revealed a significant main effect of congruence [F(1,26)=5.83, GG epsilon=1.00, partial

η^2=0.18, p < .05]. The result indicates higher μ values in the incongruent (557.58 ± 18.97 ms) compared to the congruent (547.34 ± 19.82 ms) condition. Figure 9 (A) shows the bar graph of the effect.

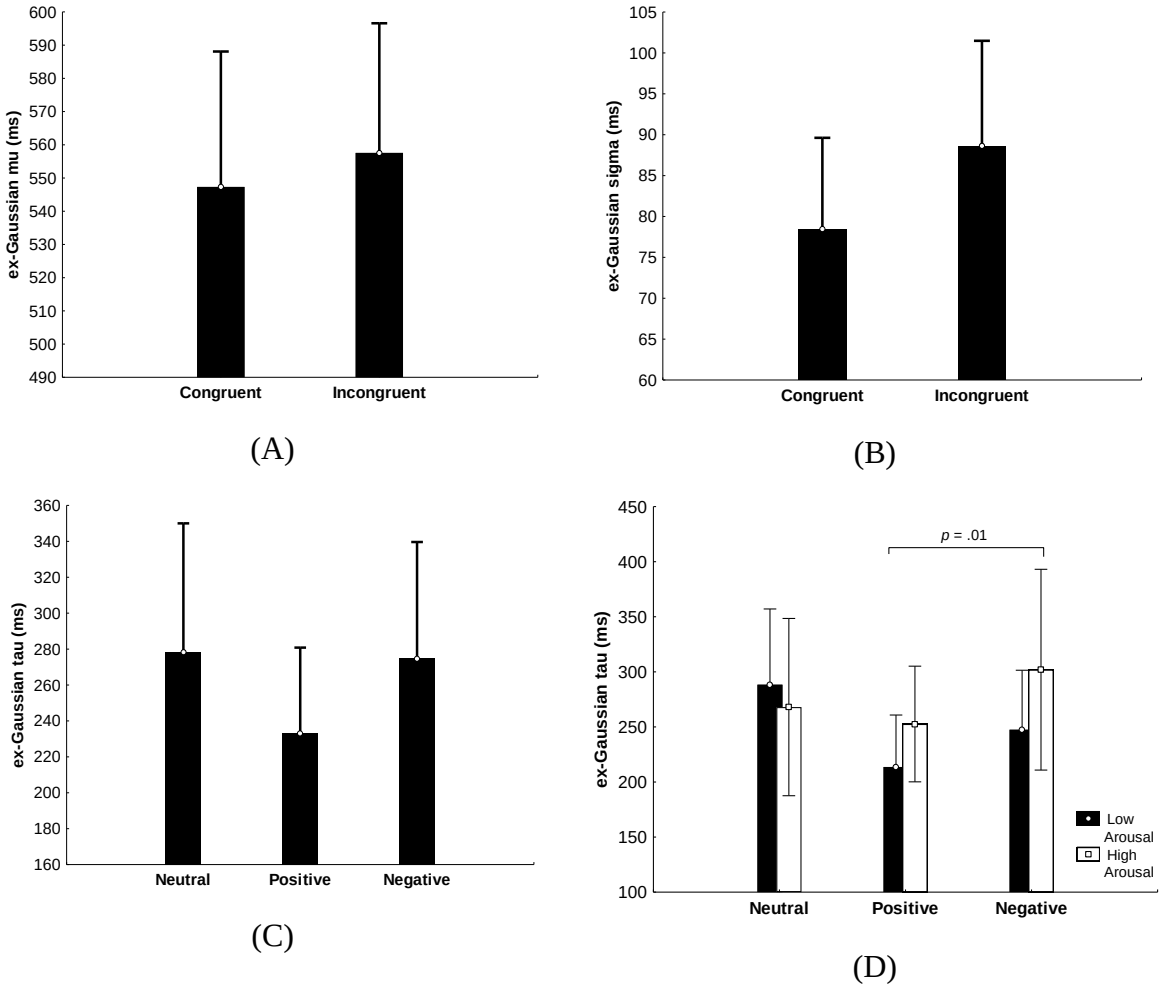


Figure 9. The isolated Gaussian and exponential components.

Bar graphs featuring the classical Stroop effect in this experiment, longer responses in the incongruent compared to congruent condition observed in the Gaussian component: (A) μ and (B) σ. Bar graphs featuring modulations of emotional context is observed in the exponential component, τ in the (C) main effect of valence and (D) valence-arousal interaction

3.2.2 The Ex-Gaussian σ: Higher σ in the Incongruent Condition

Strong evidence of a main effect of congruence for the ex-Gaussian σ [F(1,26) = 9.28, GG epsilon = 1.00, partial η^2 = 0.26, p < .01] was found in the study. Participants had a higher σ in the incongruent (88.62 ± 6.26 ms) compared to the congruent (78.46 ± 5.43 ms) condition. The results are illustrated in Figure 9 (B).

3.2.3 The Ex-Gaussian τ and Emotional Context

A three-way repeated measures ANOVA for τ revealed a trend towards statistical significance for: 1) a main effect of valence [F(2,52) = 3.31, GG epsilon = 0.69, partial η^2 = 0.11, p = .06] and 2) the interaction between valence and arousal [F(2,52) = 2.62, GG epsilon = 0.84, partial η^2 = 0.09, p = .09]. Bonferroni t confirmed significant lower τ in the low arousal positive condition compared to the high arousal negative condition (p < .05). Figure 9 (C) and Figure 9 (D) present the bar graphs of the valence and valence × arousal interaction effect, respectively.

3.3 ERP Effects

3.3.1 N200 Window: Significant Valence × Arousal Interaction

There was a significant valence × arousal interaction on the mean amplitude of the fronto-central electrodes at the N200 time window (255-305 ms). These results matched the behavioral valence × arousal interaction effects. The N200 valence × arousal ERP effect is summarized in Table 2 and illustrated in Figure 10. Post hoc comparisons showed significantly higher mean amplitude in the negative high arousal condition compared to the negative low

arousal ($p < 0.05$) and neutral high arousal ($p < 0.05$). There was no evidence of a significant ERP Stroop effect at the N200 window [$F(1,26) = 2.13$, GG epsilon = 1.00, partial $\eta^2 = 0.08$, $p = .16$].

Table 2. The N200, N450 and late negativity ERP effects table

Time Window	Effects	F	GG Epsilon	partial η^2	p
N200	Valence × Arousal	5.16	.94	.17	$< .05$*
N450	Congruence	4.90	1.00	.16	$< .05$*
Late negativity	Congruence	6.60	1.00	.20	$< .05$*
Late negativity	Arousal × Congruence	8.52	1.00	.25	<.01**

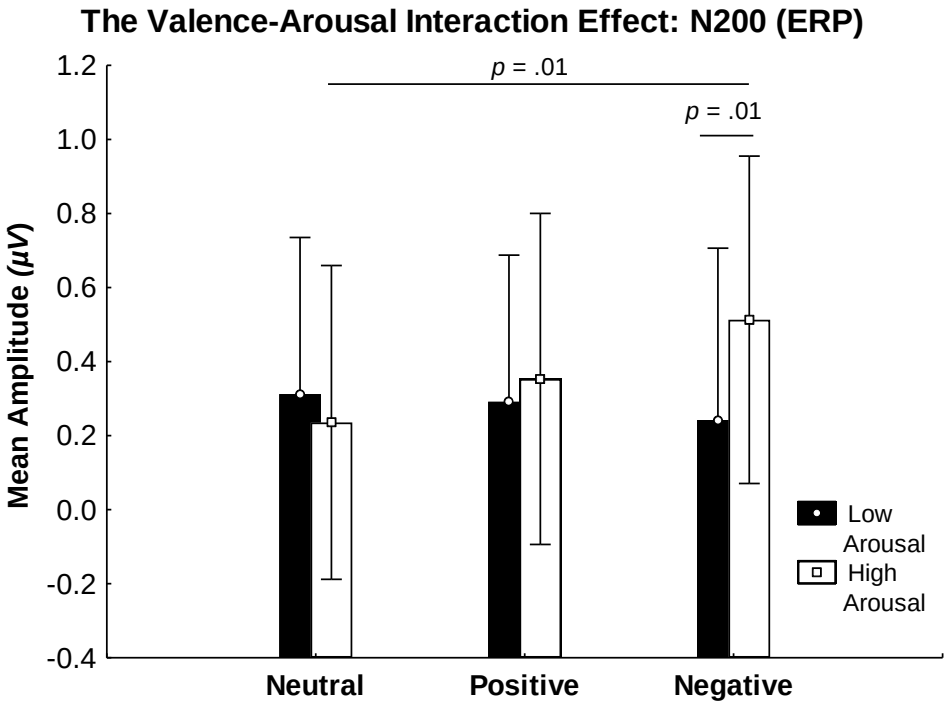


Figure 10. The N200 Valence-Arousal Interaction Effect.

The N200 mean ERP Bar Graph at the pooled fronto-central electrodes (at time window 255-305 ms) illustrate the significant interaction between emotional valence (positive, negative and neutral) and arousal (low and high)

3.3.2 N450 Window: Significant Stroop Effect

A three-way repeated measures ANOVA on the mean amplitude of the fronto-central electrodes (valence × arousal × congruence) at the N450 window revealed a significant congruence effect. There was enough evidence of stronger fronto-central negativity across all emotional conditions in the incongruent (mean ± SE; 0.19 ± 0.17 μV) compared to congruent (mean ± SE; 0.26 ± 0.18 μV) trials at the 326-426 ms window, indicating the existence of conflict relating to the task. Table 2 summarizes the congruence effect. Figure 11 depicts the bar graph of the N450 congruence effect.

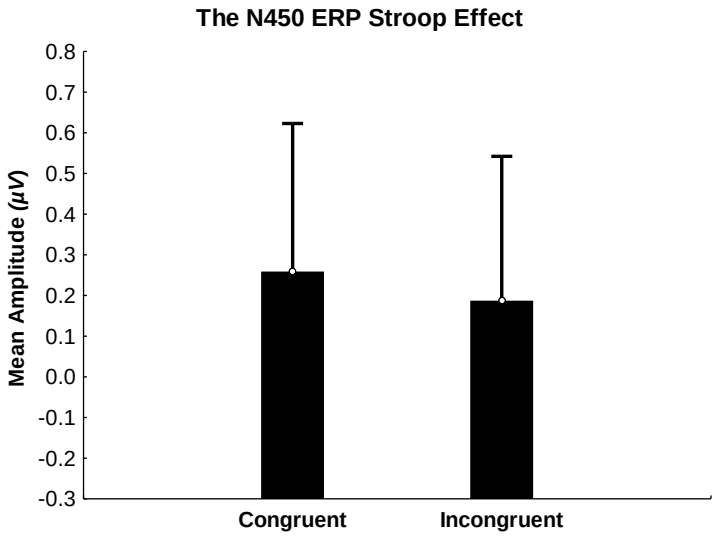


Figure 11. The N450 ERP Stroop Effect.

Mean ERP at the pooled fronto-central electrodes calculated from 326 to 426 ms, featuring the N450 ERP Stroop effect

3.3.3 Late Negativity Window: Significant Arousal × Congruence Interaction

There were two significant effects found at the 626 – 726 ms window: 1) a main effect of congruence and 2) an interaction of arousal × congruence. The ANOVA results were outlined in Table 2. The most striking result to emerge from the data is the significant stronger negativity at the fronto-central electrodes ($p < .01$) for the incongruent compared to the congruent items in the high arousal condition, affirmed by the Bonferroni t test. The result suggested an emotion-cognition interaction in ERP responses during late negativity. The bar graph of the high arousal Stroop Effect at this window is revealed in Figure 12.

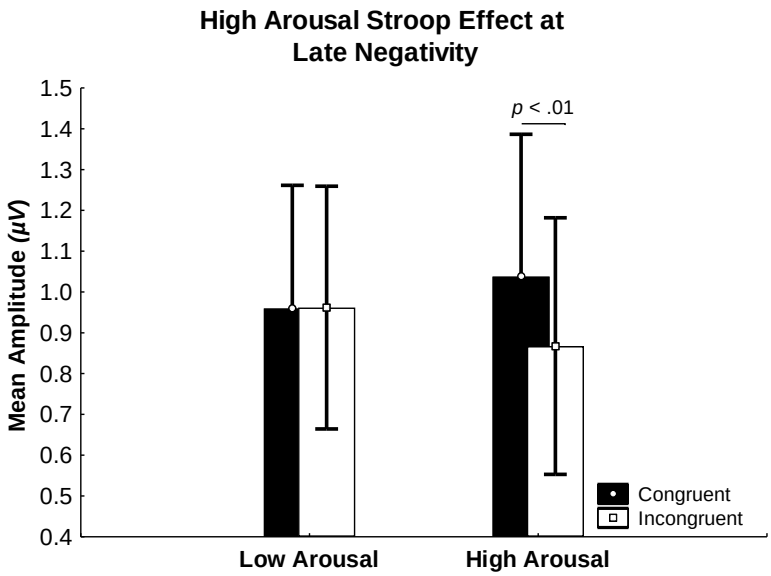


Figure 12. The Late Negativity Arousal × Congruence ERP Interaction Effect.

Mean ERP at the pooled fronto-central electrodes calculated from 626 to 726 ms during late negativity, featuring significant negative deflection in the high arousal condition

3.4 ROI Time Course Analysis with sLORETA

3.4.1 The Time Course of Neural Activity within the dACC and rvACC

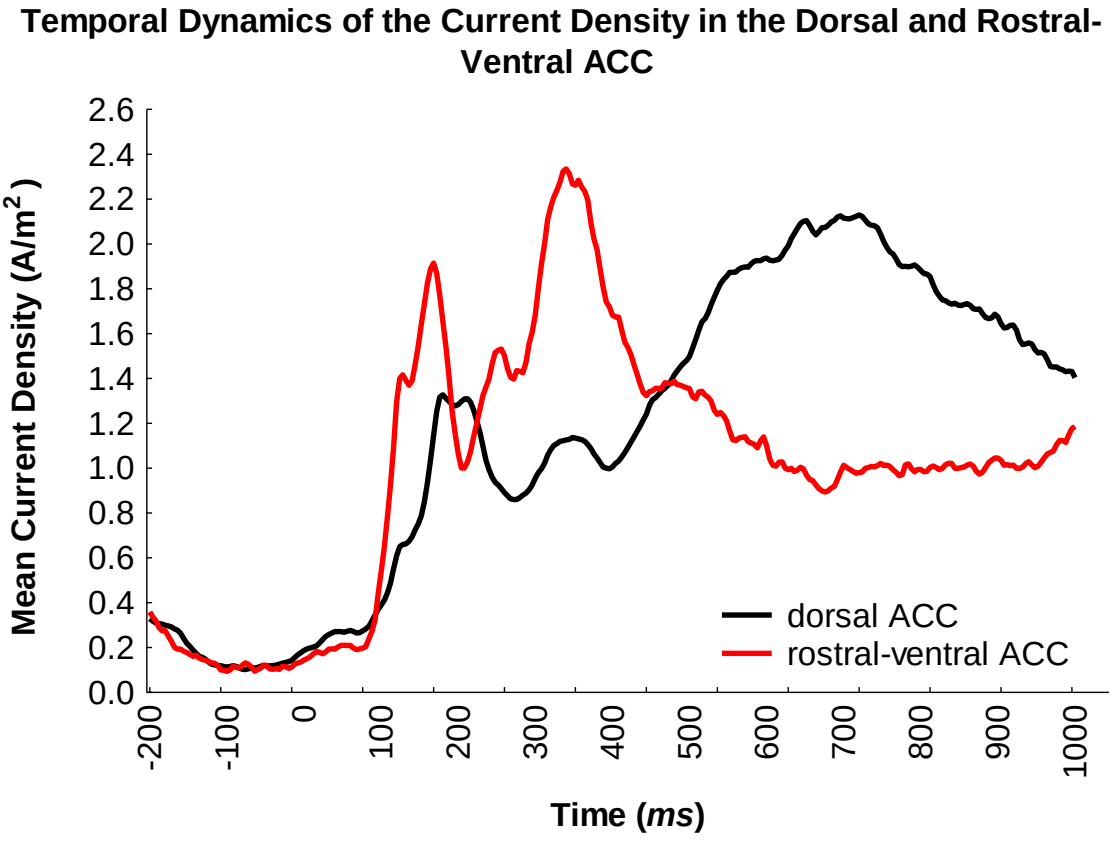


Figure 13. Time course of current source density during the emotional Stroop task, averaged across all emotional conditions.

The cortical activity at the two regions of interest (ROIs) is defined in blue (dACC) and red (rvACC). Stimuli presentation starts at 0 ms and ends when participants initiate response

The sLORETA dACC and rvACC time course activity is illustrated in Figure 13. T-test revealed a trend towards significant initial slower increase of current density within the dACC [mean difference = 32.9 ms, t (38) = 2.01, p = .055] in comparison to the rvACC in healthy subjects. It is apparent that the last peak of neural activity for each ROI was also the mode current density for the region. What stands out in the figure is the initial peaks of bursts of activity from the rvACC region that were higher in current density values but were shorter in duration compared to the dorsal region. This is especially true for the last window, which

peaked at 344 ms and started to decline soon after. Starting from 400 ms, the current density at the dACC increased steadily and peaked at 700 – 724 ms. At the late negativity window (626 – 726 ms), there was a significant increase in the current density within the dACC, compared to the N450 $[t(52) = 2.0, p < .01 \text{ (corrected)}; F(2,52) = 14.09, \text{GG epsilon} = .70, \text{partial } \eta^2 = 0.35, p < .01 \text{ (corrected)}]$ and the N200 windows $(t(52) = 2.0, p < .01 \text{ (corrected)})$. Concurrently, there was also a significant ROI effect $[F(1,26) = 21.86, \text{GG epsilon} = 1.00, \text{partial } \eta^2 = 0.46, p < .01 \text{ (corrected)}]$ at this window, indicating stronger current density in the dACC in comparison to the rvACC.

3.4.2 Valence modulated rvACC activity at N450

A three-way repeated measures ANOVA (ROI × valence × arousal × congruence) performed at the N450 window on the current density within the dACC and rvACC revealed a significant ROI × valence effect $[F(2,52) = 6.43, \text{GG epsilon} = 0.99, \text{partial } \eta^2 = 0.20, p < .01]$. Post-hoc Bonferroni t test affirmed that the difference was significant at the rvACC region. It was found that the average current density in the positive condition was significantly higher than in the negative (p = .02) and neutral (p < .01) conditions. The results were consistent with the literature and our hypothesis, suggesting that emotional valence modulated the N450 stage within the rvACC, resulting in a higher current density for the positive valence in comparison to the negative and neutral valence. The results were displayed in Figure 14 and Figure 15 in the form of a bar graph and time course source activity, respectively.

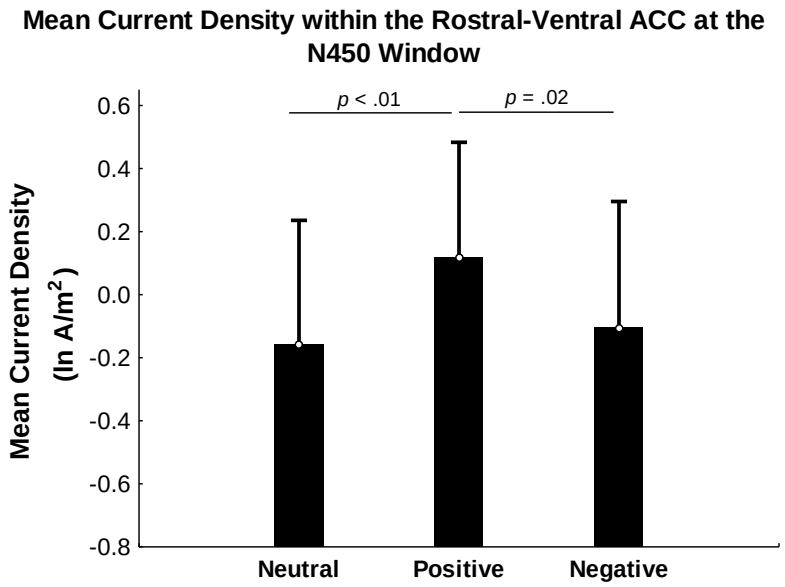


Figure 14. Valence Effect Disentangled.

Bar graph of the mean current density (unit in $\ln A/m^2$) in the rvACC at the N450 window for each valence condition

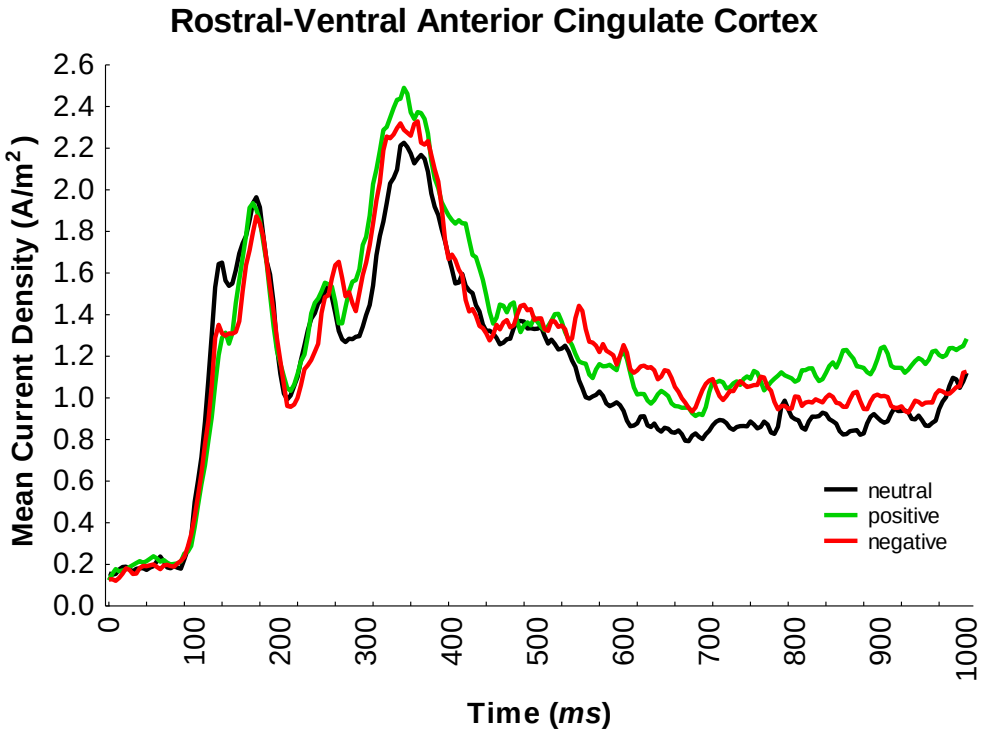


Figure 15. Average time courses of the brain responses in the rvACC for each valence condition: neutral, positive and negative.

Stimulus onset was at time=0 s. Effects of the modulation of emotional valence in the rvACC are observed at the N450 Stroop window (351-401 ms)

No significant correlation between mean RT and current density at the rvACC at this window (p = 0.68) was observed in this study. There were also no significant correlations between the ex-Gaussian parameters μ (p = 0.52 uncorrected), σ (p = 0.87 uncorrected) and τ (p = 0.90 uncorrected) and the mean current density within the rvACC.

3.4.3 Arousal modulated dACC activity during Late Negativity

A three-way repeated measures ANOVA (valence × arousal × congruence) was also performed on the current density at the dACC during the late negativity time window. The analysis was conducted because of the significantly higher activation in this ROI as compared to the rvACC region at this time window. A significant main effect of arousal was found. On average, current density in the low arousal condition was significantly higher than in the high arousal condition $[F(1,26) = 5.81,\ \text{GG epsilon} = 1.00, \text{partial}\ \eta^2 = 0.18,\ p < .05]$. Thus, emotional arousal modulated the late negativity stage within the dACC, resulting in an increased current density in the low arousal condition in comparison to the high arousal condition. Figure 16 and Figure 17 illustrate the bar graph and the time course of dACC activation of this effect, respectively.

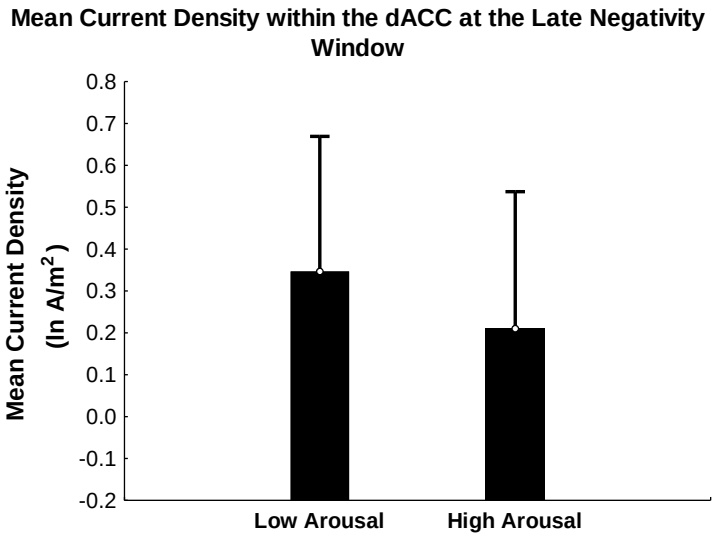


Figure 16. The Arousal Effect Disentangled.

Bar graph of the mean current density (unit in ln A/m^2) in the dACC at the late negativity window for each level of arousal

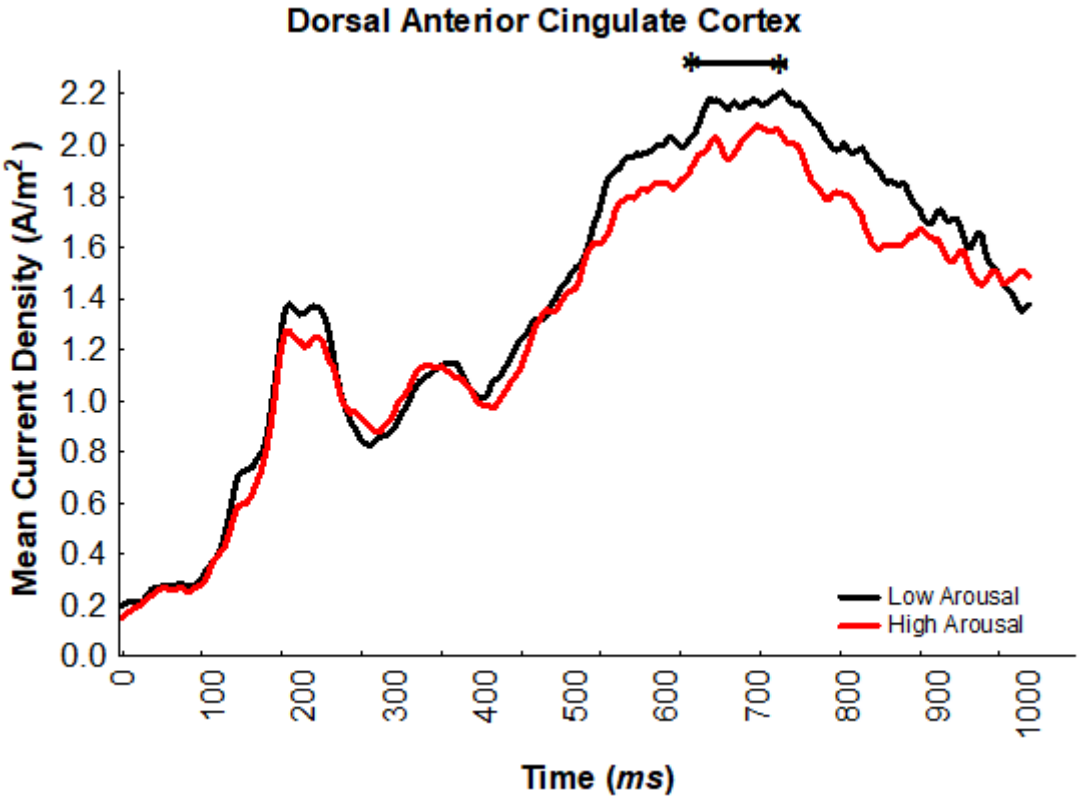
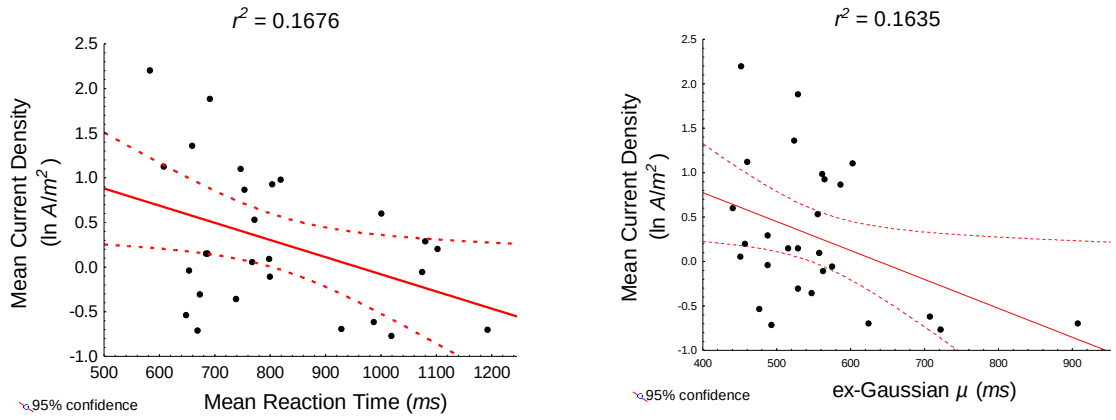


Figure 17. Averaged time courses of the brain responses in the dACC for each emotional trial type; in the low or high arousal conditions.

Stimulus onset was at time=0 s. Asterisks indicate a significant effect of the modulation of emotional arousal in the dACC at the late negativity window (626-726 ms)

3.4.4 ROI Current Density Correlates

Correlation analysis indicated a significant negative correlation between mean RT and current density at the dACC [r = -.41, p = 0.03] as illustrated in Figure 18 (A). The result suggested that the underlying current density within the dACC during late negativity was interrelated with behavioral responses.



(A) (B)

Figure 18. Scatterplots of the dACC current density with RT and the ex-Gaussian μ.
The scatterplots describe the relationship between mean current density within the dACC (vertical axis; calculated at the late negativity window (626-726 ms)) and (A) mean reaction time (horizontal axis) and (B) the ex-Gaussian μ (horizontal axis)

Correlation analysis performed between the ex-Gaussian parameters and current density at the dACC during late negativity yielded a negative correlation between the ex-Gaussian μ and mean current density at the dACC which was significant [r = -.40, p = 0.04 uncorrected] prior to the Bonferroni correction. The results, however were not significant after

correction (p = 0.12 corrected). Figure 18 (B) shows the scatterplot of the mean current density within the dACC and the ex-Gaussian μ. Furthermore, there were no significant correlations between the ex-Gaussian σ (p = 0.053 uncorrected) and τ (p = 0.34 uncorrected) with mean current density at the dACC.

4 Results from Experiment 2: Emotion-Cognition Aberrant Interaction in Patients with SZ

The second experiment investigated the impact of emotional valence and arousal on cognitive control on SZ subjects, in comparison to HC subjects using a modified emotional Stroop paradigm. Analyses on RT, ERP and sLORETA ROI current density effects were conducted using repeated measures mixed-design ANOVA with stimulus type (with factors valence (positive, neutral, negative), arousal (low, high) and congruence (congruent, incongruent)) as the within-subjects factor and group (SZ, HC) as the between-subjects factor. The Pearson product moment correlation coefficient was used to determine the relationship between behavioral effects and source activity.

4.1 Behavioral Data

4.1.1 Error rates

There were significant higher error rates in SZ subjects in comparison to HC subjects [$F(1,38) = 7.59,\ \text{partial}\ \eta^2 = 0.17, p < .01$]. The mixed-design ANOVA also revealed significant congruence × group effect on the error rates [$F(1,38) = 4.51,\ \text{partial}\ \eta^2 = 0.11, p = .04$]. The post-hoc test, however, did not reveal any significant differences. All analyses performed henceforth exclude error responses (Chajut et al., 2010b).

4.1.2 Behavioral analysis

Mixed-design ANOVA revealed significant behavioral Stroop effect across the groups [$F(1,38) = 13.68,\ \text{GG Epsilon} = 1.00, \text{partial } \eta^2 = 0.26,\ p < .01$]. Participants responded faster in the congruent (1164.54 ms, SE 88.27) compared to the incongruent (1197.07 ms, SE 91.23) condition. The significant behavioral Stroop effect across all emotional conditions demonstrated conflict elicited by task.

Further, the mixed-design ANOVA revealed that on average, SZ subjects (1512.19 ms, SE 126.79) had significantly higher RT compared to HC subjects (849.42 ms, SE 126.79; $F(1,38) = 13.66,\ ,\ \text{partial } \eta^2 = 0.26,\ p < .01$). The patient group were 78.03% slower than the HC group in the overall task.

An interesting finding from this experiment is the significant slower mean RT in the incongruent (1574.59 ms, SE 131.55) compared to the congruent items (1496.30 ms, SE 121.52; $T[df\ =\ 38] = 12.09, p < .01$) in the high arousing condition in SZ subjects. Mixed-design ANOVA on the mean RT data revealed a significant arousal × congruence × group effect [$F(1,38) = 4.50, \text{GG Epsilon} = 1.00, \text{partial } \eta^2 = 0.11,\ p < .05$]. The average Stroop effect in the high arousal condition for SZ subjects was 78.29 ms. This shows a striking 218.64% increased Stroop effect in SZ subjects, in comparison to HC subjects. The impairment was not found in HC subjects (mean RT high-arousal incongruent condition: 871.40 ms, SE 131.71; mean RT high-arousal congruent condition: 846.83 SE 121.52). Figure 19 depicts the behavioral Stroop effect in the high arousing condition in SZ subjects and HC subjects.

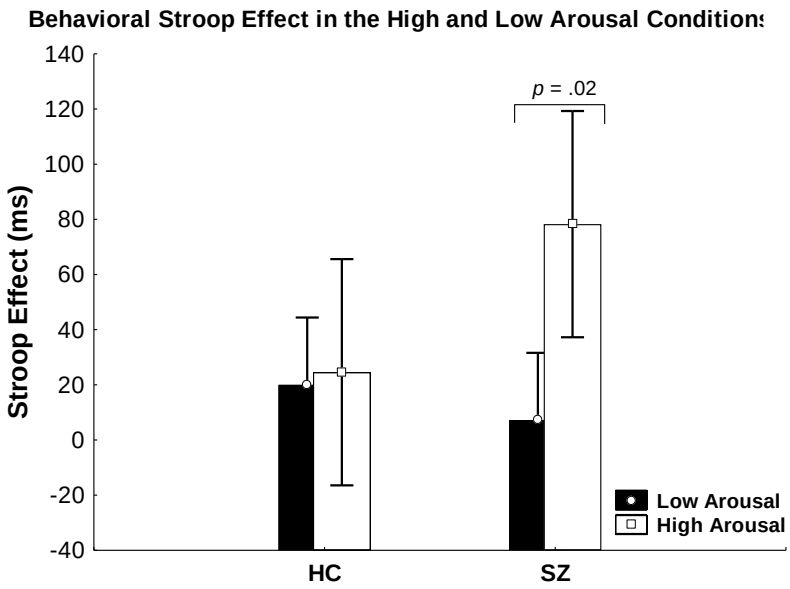


Figure 19. Arousal × Congruence Effect in SZ Subjects.

The significantly higher mean behavioral Stroop effect in the high compared to the low arousal condition in SZ subjects

4.2 ERP Effects

4.2.1 Overall ERP Group Differences

Mixed-design ANOVA revealed a trend towards significant reduction in the mean ERP amplitude at the P200 [$F(1,38)=2.98$, partial $\eta^2=0.07$, $p = .09$] and LPC windows [$F(1,38)=7.53$, partial $\eta^2=0.17$, $p < .01$] in SZ subjects, relative to HC subjects.

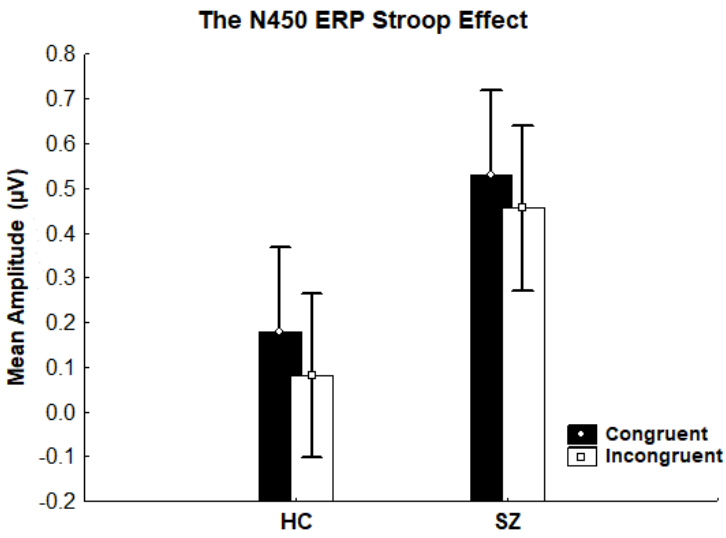
4.2.2 ERP Stroop (Congruence) Effect

There was a significant stronger negativity at the pooled fronto-central electrodes in the incongruent compared to congruent trials at the N450 window, indicating the maximization of the fronto-central regions to resolve conflict in both groups. The ERP Stroop effect at this window is summarized in Table 3 and illustrated in Figure 20 (A). The results obtained from

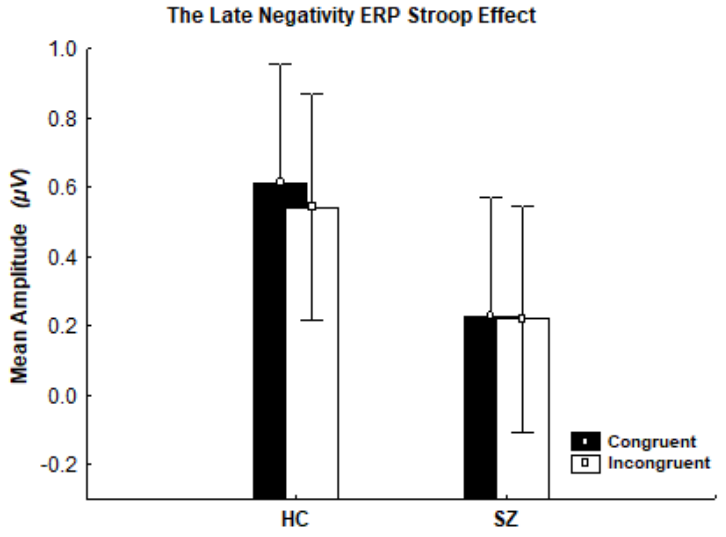
the mixed-design ANOVA revealed a 22.22% increased mean ERP Stroop effect at the N450 in HC subjects (-0.09 ± 0.03 μV) compared to SZ subjects (-0.07 ± 0.03 μV).

Table 3. The N450 and late negativity ERP effects table

Time Window	Effects	F	GG Epsilon	partial η^2	p
N450	Congruence	16.35	1.00	.30	$< .01$**
Late negativity	Congruence	3.15	1.00	.08	.08
N450	Valence × Congruence × Group	2.65	.89	.07	.08
Late negativity	Arousal × Congruence × Group	3.38	1.00	.08	.07



(A)



(B)

Figure 20. ERP Responses Describing the Stroop Effect.

(A) Mean ERP at the pooled fronto-central electrodes calculated from 326 to 426 ms indicated significant N450 ERP Stroop effect. (B) Mean ERP at the pooled fronto-central electrodes, calculated from 626 to 726 ms.

At the late negativity window, although not significant, the mean ERP Stroop effect was stronger by 91.42% in HC subjects (-0.07 ± 0.03 µV) compared to SZ subjects (-0.006 ± 0.03 µV). Figure 20 (B) illustrates the late negativity ERP Stroop effect in both, the HC and SZ group.

4.2.3 Valence × Congruence × Group Effect during N450

There was a trend towards a significant valence × congruence × group effect at the N450 window. In the HC group, post-hoc Bonferroni t comparison showed significant higher mean amplitude in the positive congruent condition (t (39.34) = 2.021, p = .047; 0.25 ± 0.20 µV) compared to the neutral incongruent condition (0.04 ± 0.21 µV). The post-hoc test did not reveal any significant differences in SZ subjects. Figure 21 provides an illustration of the ERP waves for each valence condition.

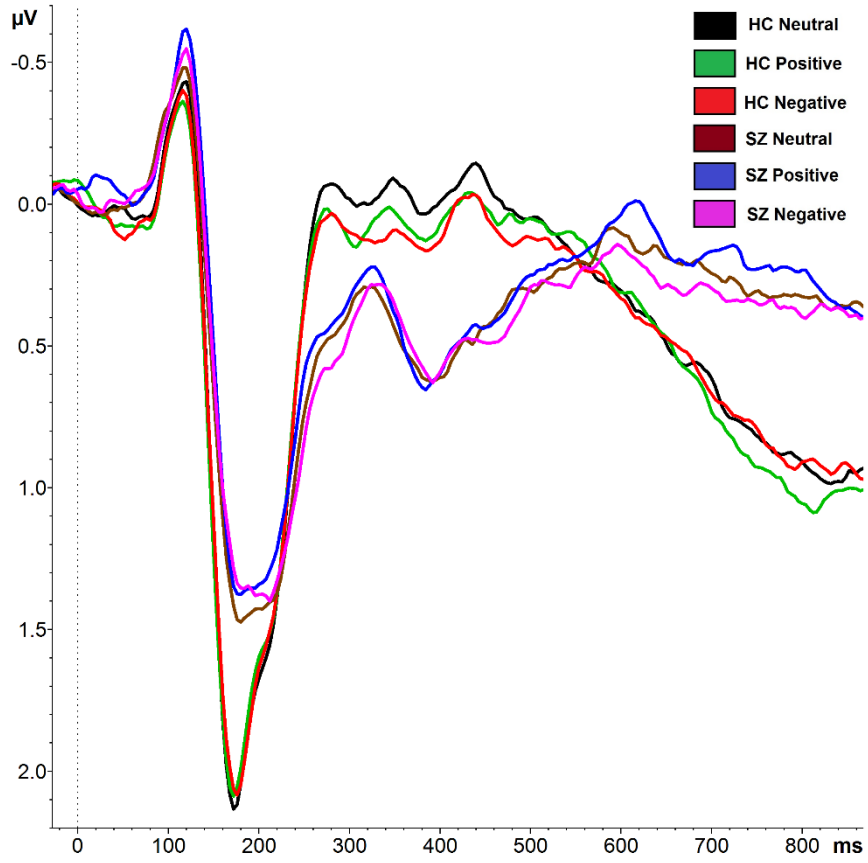
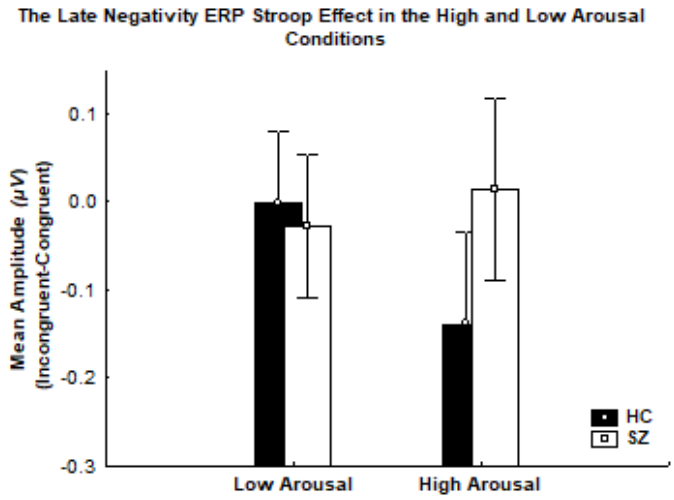


Figure 21. Valence Modulation Effect in HC but not SZ Subjects.

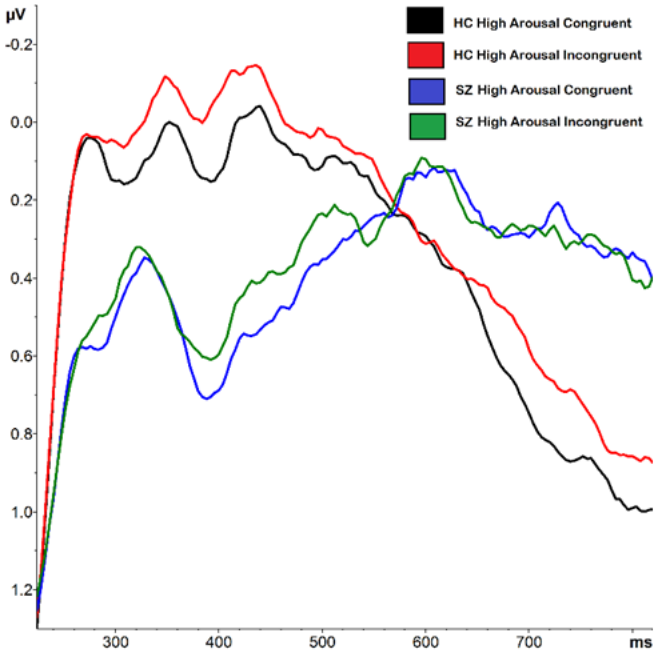
The mean ERP wave at the pooled fronto-central electrodes with respect to valence for HC (neutral (black), positive (green), negative (red)) and SZ subjects (neutral (brown), positive (blue), negative (fuchsia))

4.2.4 Arousal × Congruence × Group Effect during late negativity

Mixed-design ANOVA revealed a trend towards a significant arousal × congruence × group effect at the late negativity window. With reference to Figure 22 (A) and (B), the average Stroop effect in the high arousal condition was higher in HC subjects (-0.14 ± 0.05 μV) in comparison to SZ subjects (0.01 ± 0.05 μV) at this window. The post-hoc Bonferroni t, however, failed to gain significance.



(A)

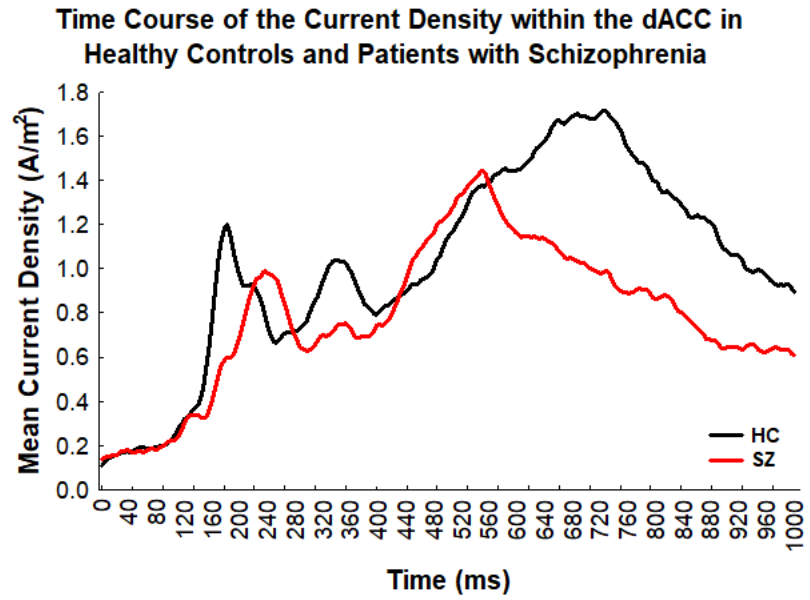


(B)

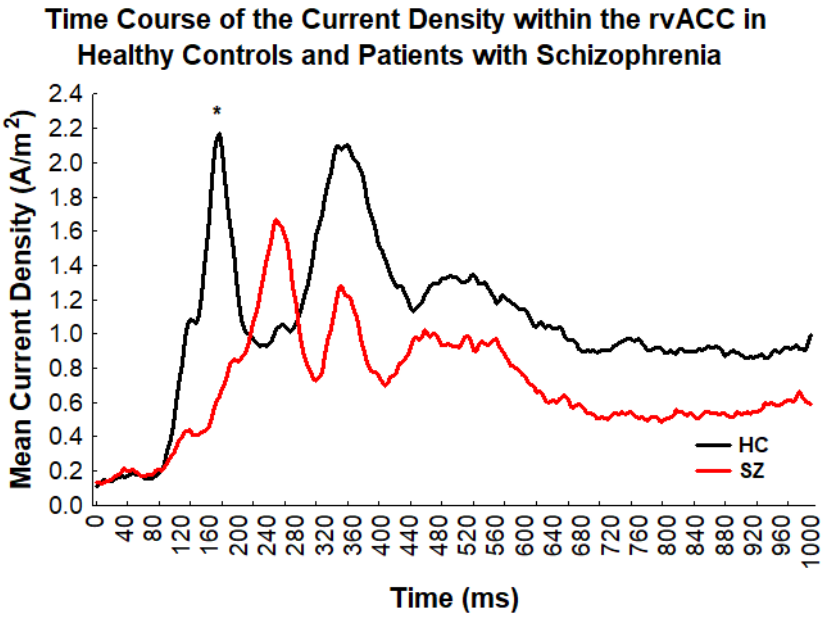
Figure 22. Arousal × Congruence Effect in SZ Subjects

(A) Bar graph of the mean ERP at the pooled fronto-central electrodes calculated from 626 to 726 ms during late negativity showed higher negative deflection in the incongruent compared to the congruent trials in the high arousal condition in the HC subjects in comparison to the SZ subjects. The difference, however did not gain significance (B) The ERP average wave at the pooled fronto-central electrodes in the high arousal congruent (HC (black) and SZ (blue)) and incongruent (HC (red) and SZ (green)) conditions. The difference between HC and SZ subjects is prominent within the late negativity window.

4.3 ROI Time Course Analysis with sLORETA



(A)



(B)

Figure 23. SLORETA current source density time course within the (A) dACC and (B) rvACC in HC subjects and SZ subjects.

Stimulus onset was at time=0 ms. Asterisk indicate significant less activation within the rvACC at 172 ms.

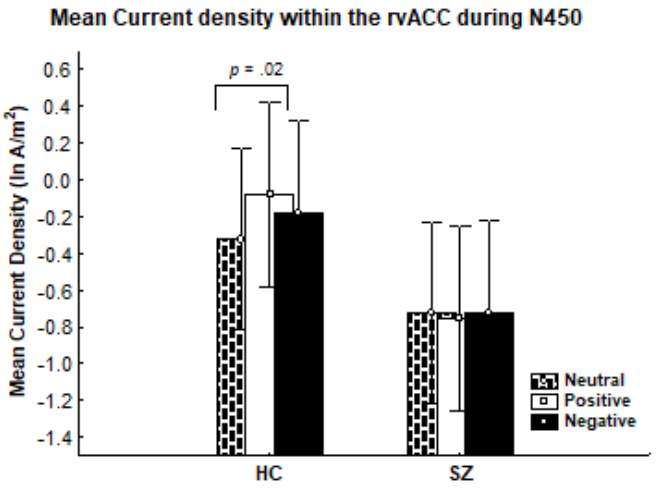
What is striking in Figure 23 (A) and (B) is the significant slower increase in current density within both the dACC [mean difference = 47.6 ms, t(38) = -2.22, , p =.03 uncorrected; .06 corrected] and rvACC [mean difference = 70.6 ms, t(38) = -2.98, p < .01 corrected] in SZ subjects. These subjects also exhibited significant less activation within the rvACC [mean difference = -1.52 A/m^2, F(1,38) =5.57, partial η^2 = 0.13, p = .02 uncorrected; .047 corrected] and the dACC [mean difference = -0.60 A/m^2, F(1,38) =5.1877, partial η^2 = 0.12, p = .03 uncorrected; .06 corrected] at the first peak of activity within the rvACC (172 ms) and the dACC (180 ms).

4.3.1 Overall sLORETA ROI group differences

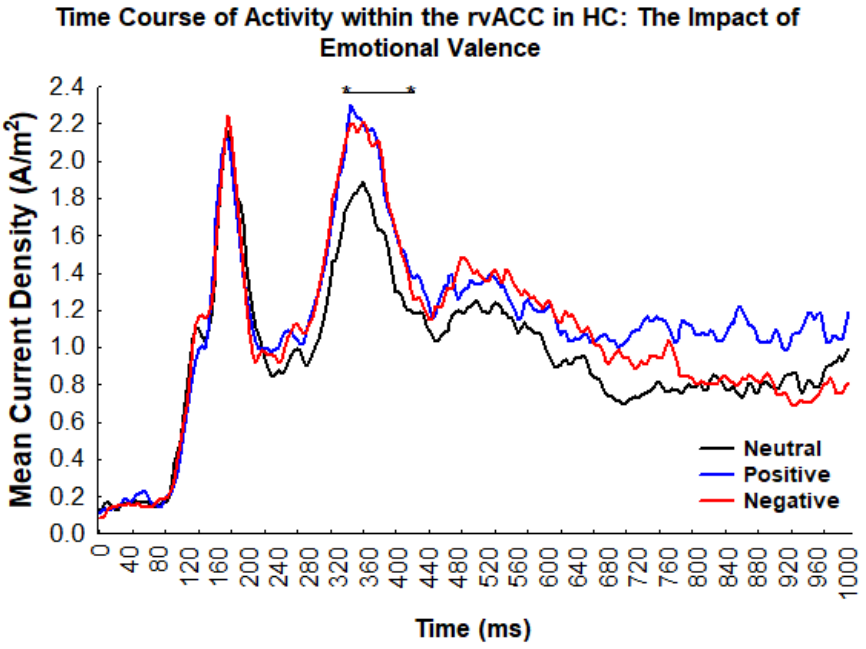
At the P200 window, mixed-design ANOVA indicated significant lower current density within both, the dACC and rvACC [$F(1,38) = 6.12, \text{partial } \eta^2 = 0.14,\ p = 0.02$] in SZ subjects, relative to the HC subjects. At the LPC window, SZ subjects had a trend towards significant lower current density compared to HC subjects [$F(1,38) = 3.03, \text{partial } \eta^2 = 0.07,\ p = 0.09$].

4.3.2 Emotional Valence modulated the N450 rvACC activity in HC but not in SZ subjects

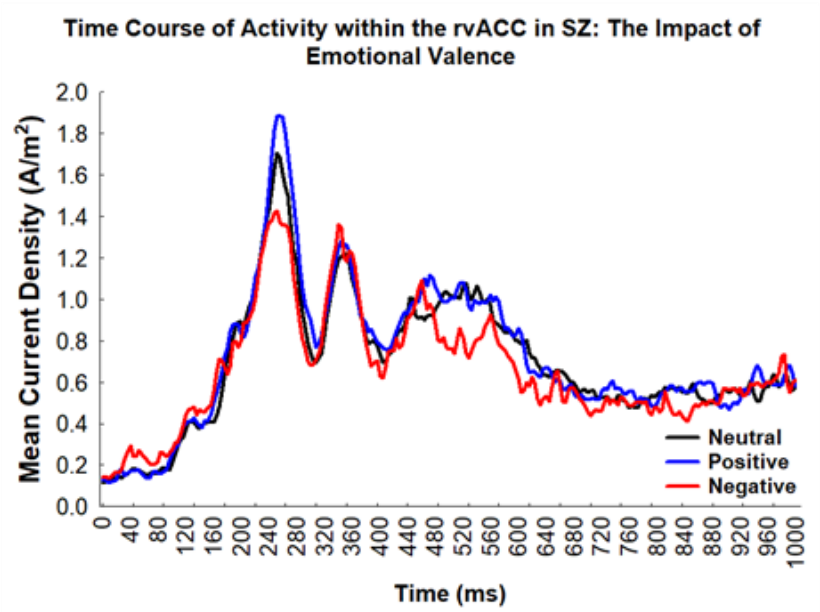
There was a significant valence × group effect at the N450 window [F (2,76) = 3.61, GG epsilon = 0.98, partial η^2 = 0.09, p < .05]. Post-hoc test indicated significant higher mean current density in the positive compared to the neutral condition (t (40.35) = 2.021, p = .02) in the HC group. This effect however, was not significant in the SZ group (p = 1.00). Figure 24 (A) to (C) exhibit the influence of emotional valence on the rvACC activity at the N450 window in HC subjects and SZ subjects, respectively.


Mean Current density within the rvACC during N450
p = .02
Mean Current Density (ln A/m²)
0.6
0.4
0.2
0.0
-0.2
-0.4
-0.6
-0.8
-1.0
-1.2
-1.4
HC
SZ
Neutral
Positive
Negative

(A)


Time Course of Activity within the rvACC in HC: The Impact of Emotional Valence
Mean Current Density (A/m²)
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0
40
80
120
160
200
240
280
320
360
400
440
480
520
560
600
640
680
720
760
800
840
880
920
960
1000
Time (ms)
Neutral
Positive
Negative

(B)



(C)

Figure 24. Valence Modulation Effect in HC but not SZ Subjects

(A) The mean ERP current density within the rvACC at the N450 window in HC and SZ subjects in the neutral (blue), positive (green) and negative (red) conditions (B) Averaged time course of the current source density within the rvACC in the neutral (blue), positive (green) and negative (red) conditions in HC subjects. Asterisks indicate a significant valence × group effect at the N450 window. (C) Averaged time course of the current source density within the rvACC in the neutral (blue), positive (green) and negative (red) conditions in SZ subjects

4.3.3 Decreased dACC activity in the high arousal incongruent condition during late negativity in SZ but not in HC subjects

At the late negativity window, the time course of the impact of the high arousal conflict condition on the dACC activity portrayed in Figure 25 revealed lower mean current density in SZ compared to HC subjects. There was a trend towards significance at the peak of the difference (of the dACC activity) between groups, at 748 ms (t (38) = 1.79, p = .08).

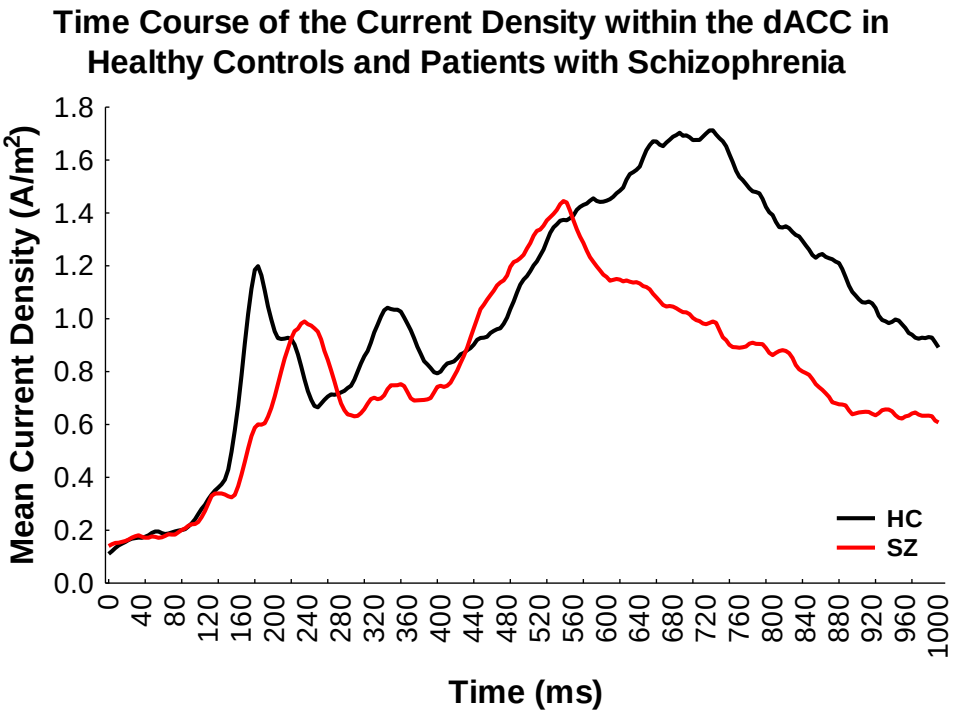


Figure 25. Averaged time course of the current source density within the dACC in the high arousal conflict condition in HC subjects (black) and SZ subjects (red)

Mixed-design ANOVA revealed an existing arousal × congruence effect within the dACC trending towards significance in the SZ group (t (39.24) = 1.96, p = .08) but not in the HC group (t (39.23) = .32, p = .35). It was found that during conflict, the mean current density in the low arousal condition was higher compared to the high arousal condition in SZ subjects within the late negativity window.

4.3.4 ROI Current Density Correlates

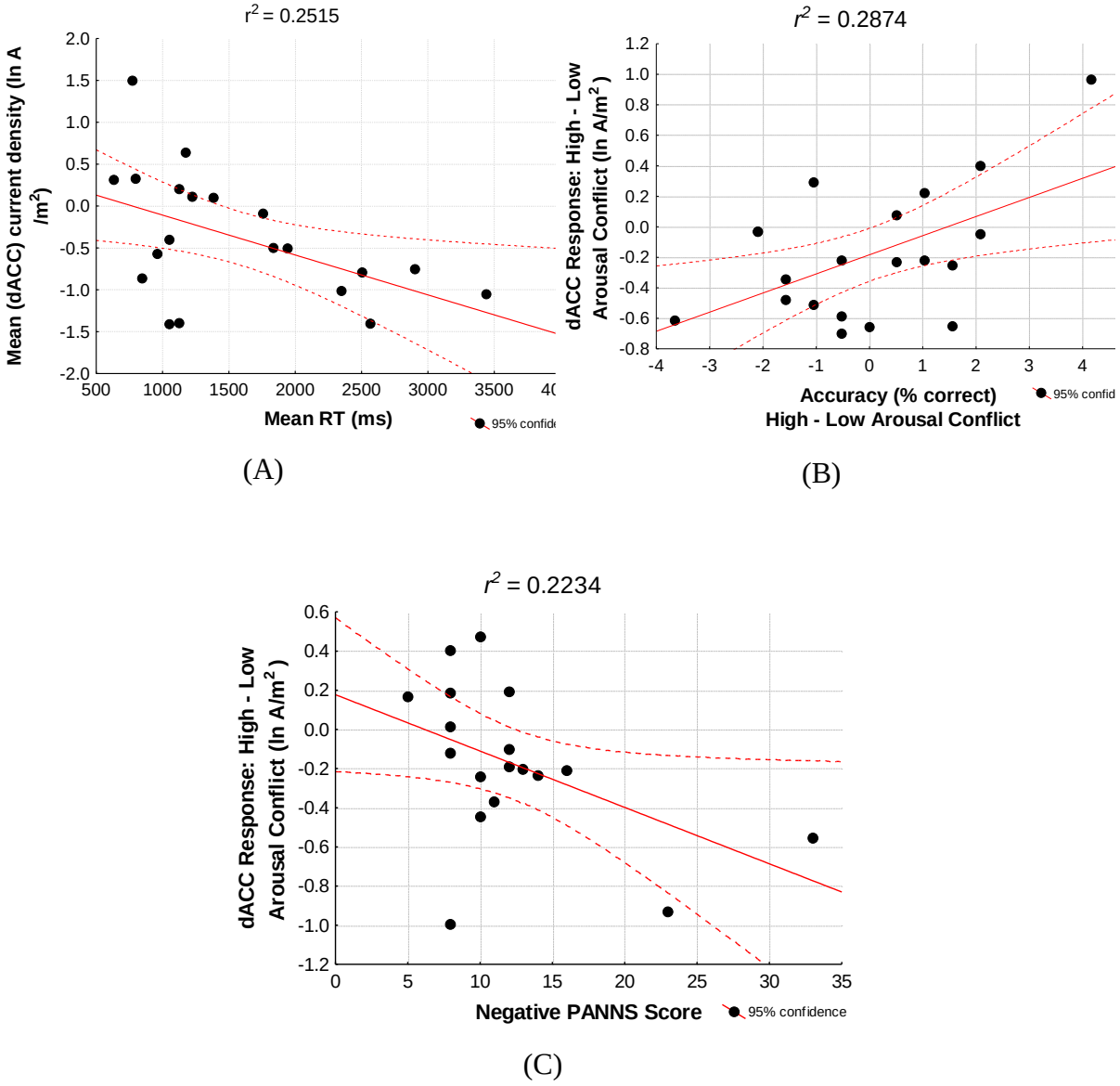


Figure 26. Scatterplots of the dACC current density with RT, accuracy and negative factor PANSS scores.

(A) Scatterplot of the mean current density within the dACC at the late negativity window and mean RT in the high arousal conflict condition. Scatterplots of the mean differential dACC responses to high arousal incongruent relative to low arousal incongruent at the late negativity window and (B) behavioral performance (accuracy) in HC subjects (C) the negative symptom factor scores of PANSS in SZ subjects.

4.3.4.1 Mean dACC at late negativity and mean RT negative correlation in the high arousal incongruent condition

There was a significant negative correlation between mean RT in the high arousal incongruent condition and mean current density within the dACC in SZ subjects [r = -.50, p = 0.024]. This result confirmed that in SZ subjects, increased mean current density within the dACC during late negativity is related with decreased mean RT in the high arousal incongruent condition. Figure 26 (A) illustrates the negative linear relationship.

4.3.4.2 Mean dACC (Differential Responses to High and Low Arousal Conflict Condition) at late negativity and accuracy positive correlation in HC subjects

At the late negativity window, the mean differential dACC responses of the high arousal incongruent and low arousal incongruent positively correlated with behavioral accuracy ($r = 0.54, p = .015$ uncorrected) in the HC subjects. The result had a trend towards significance after Bonferroni correction (p=.09 corrected). The scatterplot in Figure 26 (B) showed that higher mean dACC recruitment in the high arousal condition is associated with improved behavioral performance, relative to the low arousal condition.

4.3.4.3 Mean dACC (Differential Responses to High and Low Arousal Conflict Condition) at late negativity and negative symptoms PANSS negative correlation in SZ subjects

It is observed that the mean differential dACC responses to high arousal incongruent and low arousal incongruent were inversely correlated ($r = -0.47, p = .048$ uncorrected) to the PANSS negative symptom factor scores in SZ subjects. However, the result was not significant after Bonferroni correction (p = 2.88 corrected). It is apparent that patients with decreased mean dACC recruitment in the high arousal compared to the low arousal incongruent condition had higher PANSS negative symptoms. Figure 26 (C) presents the scatterplot of the

negative correlation between the mean differential dACC responses with PANSS negative symptom factor scores in SZ subjects

5 Discussion

The present dissertation investigated the influence of emotional valence and arousal on cognitive control in two EEG experiments. A variant of the emotional Stroop paradigm was adapted in both experiments, in which, two words (an emotional word and a color word) were presented side by side. Participants were asked to identify the ink color of the emotional word. The color word was either the same (congruent) or different (incongruent) to the ink color of the emotional word. The emotional word varied in terms of the level of valence (neutral, positive, negative) and arousal (low, high). The experiment setup allowed the assessment of conflict processing in the two dimensions of emotions. The collected behavioral, ERP and the ROI current density data yielded a coherent pattern of findings that is discussed in the current chapter.

The findings from this dissertation make several contributions to the current literature in the field of cognitive neuroscience. First, the temporal dynamics of the dACC and rvACC activation in an emotion-cognition task in healthy subjects and patients with SZ are unravelled. The time course and ERP analyses undertaken here established the N450 modulation of emotional valence within the rvACC and the late negativity modulation of emotional arousal within the dACC during cognitive control in healthy subjects. Although the time course activity initially revealed higher activation within the rvACC, at the late negativity window, there was a significant surge of activity within the dACC. Using these findings as a benchmark, SZ subjects are found to face aberrant valence modulation within the rvACC at N450 and arousal dysregulation during conflict within the dACC in relation to negative symptoms at late negativity. Furthermore, the time course activity revealed significant slower initial increase and lower peaks of time course activity within the dACC and rvACC in SZ subjects.

5.1 Study 1: Investigating the influence of emotional valence and arousal on cognitive control in healthy subjects

5.1.1 Elevated rvACC activity during earlier time intervals and significant increase in dACC activity during late negativity

Although visual inspection of the time course ROI activity showed higher initial peaks of current density within the rvACC, the most important finding in this study is the significant increase of current density within the dACC in comparison to the rvACC during the late negativity window. The current density within the dACC at this window was also significantly higher compared to the earlier N200 and the N450 windows. In addition, emotional arousal is discovered to modulate the dACC activity during late negativity in this emotion-cognition Stroop task.

This finding is well in accordance with previous fMRI and PET studies [28], [31], [32], [183]–[185] observing dACC activations during emotional and physical pain, in fear studies, during autonomic arousal and the processing of high arousing pictures. Changes in bodily arousal have also been suggested to trigger emotion and contribute to its intensity [186]. The intriguing significant higher burst of activation within the dACC compared to rvACC during late negativity could be attributed to the relation of emotional arousal to late attentional processes that engage higher order cognitive control mechanisms to overcome interference, which will be discussed in the next sections.

5.1.2 Arousal-Conflict Interaction and emotional arousal modulation on cognitive control during late negativity

Another important finding of the study was the significant emotion-cognition interaction observed during late negativity in three occurrences: 1) the significant ERP Stroop effect observed in the high arousal condition, indicating the maximization of the fronto-central regions to resolve conflict in this condition 2) the negative correlation between RT and the current density within the dACC, indicating a demand for more resources within the dACC with faster RT in this window, in line with findings of [154], [187] 3) the significant negative correlation between the dACC activity and the ex-Gaussian μ, which mainly indexes response conflict. It could be speculated that the significant ERP Stroop effect in the first occurrence is related to the extra effort required during conflict resolution in the high arousal condition in line with the findings of (Demanet et al., 2011; Most et al., 2007; Padmala et al., 2018). These findings have important implications of revealing the functional significance of the late negativity waveform modulations by arousal. It is highly probable that emotional arousal modulated dACC activity in the context of concomitant cognitive demands during late negativity.

The current study isolated the effects of response conflict and task conflict in the emotion-cognition Stroop task using the ex-Gaussian method. The classical Stroop effect in this experiment is observed in the Gaussian components (μ and σ) similar to findings of [141], [174]. These results are consistent with previous research (Monsell et al., 2001; Steinhauser and Hübner, 2009) linking the ex-Gaussian μ with interference from response conflict. Mapping the correlates of the ex-Gaussian μ and source activity relate interference from response conflict with dorsal activity which is observed during late negativity. On the other

hand, the main effect of emotional valence is observed in the exponential component (τ) in this study.

In (Monsell et al., 2001; Steinhauser and Hübner, 2009), attentional bias towards emotional salience is found to be caused by interference from task conflict. The results in this study is in agreement with (Moreno-Cid et al., 2015) which shows emotional context differences observed in the exponential component with regards to emotional valence. An important implication of these findings is the ability to distinguish the effects caused by the cognitive Stroop interference in relation to the Gaussian components, μ and σ and emotional interference in relation to the exponential component, τ would not have been possible with the analysis of mean RT and error rates alone. Future emotion-cognition studies may benefit immensely by implementing the ex-Gaussian analysis.

5.1.3 Emotional valence modulation on cognitive control during N450

The current study extends previous experimental findings (Chiu et al., 2008; Shafritz et al., 2006) regarding the modulation of emotional valence at the rvACC to the Stroop literature. rvACC current density was higher in the positive compared to the neutral and negative conditions. Furthermore, it was found that emotional valence enhanced overall performance with faster RT in the positive compared to neutral condition, in line with (Schmitz et al., 2009). Within the N450 window, we observed the classical cognitive ERP Stroop effect with stronger negativity in the incongruent responses at fronto-central electrodes indicating the association of the N450 amplitudes with cognitive conflict. It seems possible that the modulation of emotional valence, concurrent with the N450 Stroop effect is due to interference caused by stimulus conflict from reading the task-irrelevant emotional word valence (Coderre et al., 2011; Monsell et al., 2001).

5.1.4 Interrelation of emotion-cognition and distinction of valence-arousal related processes within the ACC

Within discussions of the functional profile of brain regions involved in emotion-cognition studies, controversy of distinct emotion processing via the "hot affective" rvACC and cognitive processing via the "cold cognitive" dACC is ubiquitous (Bush et al., 2000; Mohanty et al., 2007; Perlman and Pelphrey, 2010)**.** However, recent literature have indicated that emotion and cognitive processes are mutually dependent and integrated in the brain (Etkin et al., 2011; Inzlicht et al., 2015; Pessoa, 2017). Although scientific debates such as these are necessary to unveil the truth, a far more important issue of distinguishing the impact of the valence and arousal dimensions of emotions in modulating cognitive control is obscured, as previous studies found distinct time intervals and brain regions involved during these modulations. Based on the results of this study, we observed that emotion-cognition processes are interrelated in the brain, but valence and arousal are processed separately via the N450 rvACC valence modulation and late negativity dACC arousal modulation that initiated response conflict resolution, in line with (Inzlicht et al., 2015).

The latter finding provide some support for the conceptual premise of Arousal-Biased Competition (ABC) (Mather and Sutherland, 2011). This model amplifies the competitive advantage of the high-arousing emotional content over the ink color of the words, causing priority in processing resources, regardless of whether this information has priority. Although this diverts processing away from the incongruent color word for enhanced conflict resolution, it may cause distraction towards the goal of responding to the ink color of the word. In healthy subjects, activated by arousal and conflict, the dACC may help to counter emotional distraction

by activating top-down goal-directed conflict resolution. Thus, when emotion coincides with cognition, the late window, susceptible to arousal, causes diminished positivity in the high arousing incongruent condition (Olofsson et al., 2008) and engages in conflict resolution.

A neurobiological theory (Ashby et al., 1999), developed to explain the benefits of positive emotions on cognition surrounds the premise that positive emotions mediates the release of dopamine in brain regions associated with cognitive processing, such as the ACC, leading to increased performance in emotion-cognition tasks (Nittono et al., 2012; Subramaniam et al., 2009; Van der Stigchel et al., 2011). This effect has been associated with modulations of earlier time windows (Van Wouwe et al., 2011; Wiswede et al., 2009; Xue et al., 2013) and has been connected with the processing of affective salience, in line with the results of this study. Taken together, both premises suggest that the modulation of affective salience occurs at an earlier window, while the modulation of emotional arousal driving the top-down processes of controlling response selection occurs at a later time interval in the emotion-cognition Stroop paradigm.

5.1.5 General Discussion

In general, emotional valence modulated cognitive control at an earlier N450 time window, possibly due to initial selective attention towards emotional word valence. Emotional arousal modulated the late negativity window, which initiated response resolution. The modulation of emotional arousal during a later window (late negativity) and the modulation of emotional valence during an earlier window (N450) matched those observed in previous ERP (Olofsson et al., 2008) and ERP microstates studies (Gianotti et al., 2008). One speculation that could be made in this study is the initial higher peaks of rvACC activity is caused by valence (salience) detection from task conflict, meanwhile the later significant increase of dACC

activity from the arousal modulation initiated response selection. The empirical findings of this study provide a benchmark for comparing the time courses and modulations of emotional valence and arousal of patients with SZ and matched HC in Study 2. Future clinical studies involving patients suffering from psychiatric conditions such as anxiety, borderline personality disorder, PTSD and depression might benefit vastly from the discoveries made in the current study.

5.2 Study 2: Emotion-Cognition Aberrant Interaction in Patients with SZ

5.2.1 Hypoactivation of the dACC activity associated with cognitive deficiency in SZ subjects during late negativity in the high arousing condition

The most interesting finding in this study is the hypoactivation of dACC activity at the late negativity window (626-726 ms) in the high arousal conflict condition with concomitant cognitive deficits in SZ subjects. This is in accordance with the hypothesis of the study. Plausible differences between HC and SZ subjects within the late negativity window were determined in two occurrences: (1) the ERP differential activity in the high arousal incongruent relative to the high arousal congruent condition exhibiting higher ERP Stroop effect in HC compared to SZ subjects. An implication of this condition is the possibility that the maximization of the fronto-central regions during late negativity aided the HC subjects during conflict resolution, but not the SZ subjects in this study; and (2) a general decline of activity within the dACC starting from 560 ms and persisting to the late negativity stage in SZ subjects in the high arousal conflict condition.

The lower underlying current density within the dACC in SZ subjects at this window is interrelated with impaired performance in the high arousal conflict condition. This accords to previous EEG and fMRI studies (Phillips et al., 1999; Williams et al., 2004) which shows reduced ACC activity in the high arousal condition, in contrast to the low arousal condition in SZ subjects. The results of the study bridged the gap between fMRI findings (Dichter et al., 2010) linking dACC hypoactivation in aversive condition with cognitive impairment and findings from (Das et al., 2007; Kaneko et al., 1992; Williams et al., 2004) linking dysregulation of emotional arousal within the dACC, associated with cognitive deficits in SZ subjects. In addition, the current study detected the time window of the high-arousal dACC hypoactivation which is linked to cognitive deficits in SZ subjects.

The study has exhibited that increased processing resources within the dACC during late negativity, engaged by the high arousal emotional words enhanced task performance in HC subjects. Within the same time window, results show existing arousal-conflict interaction impairment in SZ subjects with higher negative (PANSS) symptoms. This combination of findings provide some support for the premise that SZ subjects with higher negative PANSS symptoms utilized less processing resources within the dACC resulting in impaired task performance in the high arousal conflict condition. Results of the current study also support the findings of hypoactivation within the ACC in SZ subjects with high negative PANSS symptoms in fMRI studies such as (Dichter et al., 2010) with aversive stimuli and (Nelson et al., 2015) with pleasant stimuli.

An interesting possible explanation for these combination of findings are that the inadequate emotion-cognition integration and interaction within the ACC in SZ subjects resulted in reduced goal-directed behavior and further exhibited as negative symptoms (Yücel et al., 2003). A different perspective in (Schell et al., 2005) suggests that negative symptoms

are presented as a method of surviving high arousal situations, such as attempts to suppress reactions to high arousing stimuli in SZ patients. It is possible that the results here would fit the neural diathesis-stress model (Nuechterlein and Dawson, 1984; Pruessner et al., 2017; Walker and Diforio, 1997). The model hypothesized that HPA axis dysfunction in SZ subjects foster negative symptoms and further heighten cognitive impairments. These findings might also be in line with the DA hypothesis of SZ which associates prefrontal hypodopaminergia (Howes and Kapur, 2009) with hypofrontality (linked with the hypoactivation of the ACC in SZ subjects (Mientus et al., 2002)) and with negative symptoms and cognitive deficits in SZ.

It could be speculated that in this study, SZ subjects experienced an escalation of emotional arousal in the high arousing conflict condition in comparison to HC subjects, requiring significant higher RT to complete the task. SZ subjects may struggle to inhibit irrelevant responses (e.g. due to the narrowing of attention (Kahneman, 1973), search for the meaning of their arousal (Clamor et al., 2015), face increased lability of attention allocation (Kahneman, 1973) and disengage from the emotional stimuli. This struggle might be especially predominant in SZ subjects with high negative symptoms (Strauss et al., 2011) because the task-irrelevant high arousing word might cause weakened ability to inhibit (Braver et al., 1999) the incongruent color word. An implication of this is the possibility that SZ subjects with decreased negative symptoms recruited more dACC activity during late negativity that probably helped them overcome the conflict in the high arousal items.

5.2.2 The impact of emotional valence on rvACC activity in SZ subjects

Previous studies evaluating the influence of emotional valence during conflict in patients with SZ observed inconsistent results. The current study found that emotional valence modulated both the ERP and rvACC activity within the N450 window in HC subjects but not

in SZ subjects. The nonsignificant N450 valence effect in SZ subjects is likely to be caused by increased neural activations to neutral stimuli, as reported in (Habel et al., 2010a; Murray et al., 2008) (also see (Potvin et al., 2016) for a review). It is also critical to note research that show male SZ subjects to report higher levels of arousal (Llerena et al., 2012) and stronger aversion (Cohen and Minor, 2010) towards neutral stimuli. It is therefore likely that the condition might lead to the impairment in discriminating relevant from irrelevant aspects of stimuli. These findings could be associated with the DA hypothesis in patients with SZ (Howes and Nour, 2016; Kapur, 2003) that associates increased striatal DA with aberrant assignment of salience to a stimulus (Howes and Kapur, 2009). Indubitably, the disruption of emotional valence modulation within the rvACC at the N450 window in SZ subjects add to a growing body of literature on SZ research.

5.2.3 Time Course aberration in SZ subjects: slower initial activation and decreased peaks of activity

The present study has demonstrated, for the first time that SZ subjects had significant slower initial activation and decreased peaks of activity within both, the dACC and rvACC across conditions, in contrast to matched HC. These results suggest timing deficits and hypoactivation within both, the dACC and rvACC in SZ subjects. It can therefore be assumed that the abnormal regulation of emotion-cognition circuits led to impaired performance in SZ subjects in this study. These results support previous research of the time course of fMRI hemodynamic responses (Dichter et al., 2010) of the anterior cingulate gyrus (ACG) in target conditions, that showed slower initial activation in SZ subjects. The significance of attaining the time course activity between these regions is that it provides an accurate general view of the activation and underlying temporal neural mechanisms of emotion-cognition interaction in SZ subjects, which is still not well understood.

6 Perspectives

6.1 Critique

6.1.1 Limitations

In conducting this study, several limitations have been recognized. The time course analysis portrays the advantage of EEG based source localization in comparison to both sensor level EEG or ERP analysis (Luck, 2012; Pascual-Marqui et al., 1994) (temporal activity between our ROIs could not be achieved using these methods alone) and to fMRI (Aine, 1995; Mulert et al., 2004) (due to its limitations concerning its temporal resolution). However, the poor spatial resolution of EEG distorts the recovered time course of the underlying sources at scalp level. The EEG-fMRI method (Boksem et al., 2005) could be a possible solution to this limitation.

One of the issues that emerged from the experiment is the valence and arousal ratings of the word stimuli were not reviewed by the patient group. This is in accordance to previous emotional Stroop studies (Demily et al., 2010; Roux et al., 2010; Wiffen et al., 2014) and word-related studies (Klumpp et al., 2010; Strauss et al., 2011) where separate valence and arousal patient (SZ) ratings were not performed. Further, studies such as (Bonin et al., 2003; Herbener et al., 2009; Jalenques et al., 2013) have shown that SZ subjects have preserved perception towards the valence and arousal levels in emotional word. However, it should be noted that studies such as (Cohen and Minor, 2010; Llerena et al., 2012) reported differential valence and arousal related emotional experience in SZ subjects, in comparison to HC subjects. To ensure enhanced experimental control and similar emotional experience between both the SZ and HC groups, future studies should obtain subjective evaluation of the valence and arousal levels of

the stimuli as well as the current mood state of SZ subjects. In order to avoid repetition effects in the results of the experiment, this procedure should be done after the main experiment. However, the effects will then be present in the ratings. In addition to the subjective ratings, it would also be helpful to have other objective measures of emotional salience of items. Arousal predisposition trait test (Clamor et al., 2015), measuring hyperarousal in SZ subjects using GSR or EDA (Pincus and Tucker, 2002; Schell et al., 2005)**,** tracking EMG measurements (Pincus and Tucker, 2002) and taking pulse rate (Pincus and Tucker, 2002) could be possible measures.

6.1.2 The Behavioral Stroop Effect in Study 1

6.1.2.1 A comparison of Stroop (1935) with the current experiment

A critical point may arise from our results due to the marginal behavioral Stroop effect found in Study 1, in comparison to the 47 s Stroop effect found by J.R. Stroop (Stroop, 1935) in his second task. This finding is interesting, but not surprising as the response measures in (Stroop, 1935) were obtained orally, causing higher Stroop interference (Penner et al., 2012) compared to computerized, fully automated studies. It should be noted that this transition, also, was from listed to single stimuli presentation.

Contrary to the experiment in this dissertation, the experiment in (Stroop, 1935) was composed of two conditions: squares of colors and color words in an incongruent ink. The instructions given to the participants were similar to both Study 1 and Study 2, where participants were asked to name the ink colors as quickly as possible and ignore the meaning of the words. However, the participants were also asked to correct all errors. In the instance of

higher error rates in the incongruent condition, this procedure may lead to increased Stroop effect.

Further, the effect of practice has been found to reduce interference. Although still sizeable, Stroop's third experiment [38] showed reduced Stroop effect (to 8.1 s) during the final session, as a consequence of practice. The high number of trials in this study, due to the requirements of an ERP experiment and due to the number of conditions in the study may lead to mental fatigue and reduced Stroop effect. Another possible explanation of the marginal Stroop effect found in Study 1 is the dilution of the Stroop effect by the color-irrelevant stimuli in this study. In (Kahneman and Chajczyk, 1983), the Stroop effect is diluted by half when a neutral word is added to the display of color patch and color word presented simultaneously.

6.1.2.2 How do RT distributions affect the behavioral Stroop effect?

Due to the outliers (extreme values), RT distributions are generally skewed to the right, similar to the ex-Gaussian distribution (Heathcote et al., 1991; Ratcliff, 1993; Whelan, 2008). Outliers have been, at times, deleted by researchers using methods such as trimmed mean. As a consequence, these methods acquire higher statistical power compared to the traditional RT analysis (Ashley and Swick, 2009; Besner et al., 1997; Egner et al., 2008; MacDonald, 2000; Roberts and Besner, 2005). The Median Absolute Deviation (MAD) is a robust method in trimming outliers (Leys et al., 2013). With the implementation of this method in Study 1, the two-tailed repeated measures ANOVA test on the RT is successful in acquiring a significant behavioral Stroop effect [$F(1,26) = 13.19$, GG epsilon $= 1.00$, partial $\eta^2 = 0.34$, $p <$ .01]. Congruent trials [747.30 ± 27.47 ms] were responded to faster than incongruent trials [760.47 ± 26.77 ms] across all emotional conditions demonstrating conflict elicited by task. A

note of caution when implementing data trimming methods is that researchers lose useful behavioral information (Ratcliff, 1993; Whelan, 2008) by deleting the outliers.

Stroop studies such as (Badzakova-Trajkov et al., 2009; Fan et al., 2003; Hanslmayr et al., 2008; Perlstein et al., 2006) reported behavioral findings using median RT in order to eliminate the influence of outliers. Implementing this method in a two-tailed test, the median RT for each participant in Study 1 were calculated and delivered to repeated measures ANOVA with factors (valence × arousal × congruence), eliciting a significant behavioral Stroop effect, i.e., congruent trials [727.67 ± 25.85 ms] were responded to faster than incongruent trials [743.15 ± 25.64 ms] across all emotional conditions [$F(1,26) = 27.25$, GG epsilon $= 1.00$, partial $\eta^2 = 0.51$, $p < .01$] demonstrating conflict elicited by task. Although this is a rather encouraging finding, it is notable that median RT is a biased estimation of the population median (Miller, 1988; Whelan, 2008).

A recommended alternative (Heathcote et al., 1991; Lacouture and Cousineau, 2008; Ratcliff, 1993) to the traditional mean RT analysis is to examine the whole RT distribution itself. The ex-Gaussian distribution has been used in many studies such as (Heathcote et al., 1991; Lin et al., 2013; Penner-Wilger et al., 2002; Steinhauser and Hübner, 2009; van Belle et al., 2015) to successfully summarize RT experimental data. Because of this, the ex-Gaussian method was incorporated in the behavioral analysis of Study 1, resulting not only in the established Stroop effect of the ex-Gaussian μ and σ, but also in the attainment of a functional profile of the valence and arousal modulation during cognitive control in healthy subjects.

6.1.3 Lack of Valence-Conflict Effect in Study 1 and Study 2

A caveat to the results of Study 1 is that the behavioral valence and arousal related congruence interaction effects did not gain significance in the repeated measures ANOVA as

well as in multiple comparisons. Further, there is no significant valence-conflict effect in brain responses. It is possible that these effects would gain significance if the sample size of the study is increased thus maximizing statistical power (Murphy and Myors, 2008). The problem could also be solved by conducting separate arousal-congruence and valence-congruence studies, which are liable to reduce the order effect (Boksem et al., 2005).

In Study 2, including both valence and arousal dimensions have helped in the detection of arousal-conflict behavioral deficiencies suffered by SZ subjects. However, there were no significant valence-related conflict effects found in the study. It was discussed in (Anderson, 2005) that in comparison to valence, arousal plays a more important part in determining the degree to which emotional stimuli impact cognition. This provides some explanation as to the lack of valence-conflict effect in both, Study 1 and Study 2. It has to be noted, however, that a larger sample size would afford increased power to detect possible valence-conflict effect.

6.1.4 Strength of stimuli in manipulating participants' emotions

Although emotional words have been successfully used to modulate brain activity (Li et al., 2007; Ortigue et al., 2004; van Hooff et al., 2008), a disadvantage of using word stimuli is that the intensity may not be strong enough to generate robust interference, in comparison to visual stimuli. An implication of this is the possibility to enhance the cognitive interference from emotional stimuli by using visual stimuli to provoke/increase interference.

6.1.5 Push-Pull Model as a possible explanation to the temporal dynamics of dACC and rvACC?

One question that needs to be asked is whether the initial higher rvACC activations and the stronger current density within the dACC in comparison to the rvACC activity during late negativity could be explained by the push-pull model between "cold" cognitive regions and "hot" affective regions. The push-pull relationship (Pessoa, 2013) between "hot" emotional and "cold" cognitive regions are usually associated with emotion-cognition tasks and has been found in several studies (Drevets and Raichle, 1998; Goel and Dolan, 2003; Van Dillen et al., 2009). Interestingly, this phenomena has also been observed in pure cognitive experimental studies (Hsu and Pessoa, 2007).

Further evidence indicates negative correlation between the dACC – based frontoparietal attention networks and the rvACC – based affective networks in an fMRI resting state functional connectivity analysis (Margulies et al., 2007). It is tempting to justify our results in terms of the emotion-cognition push-pull theory which implies that emotion and cognition resources are competitive; i.e. emotional processing decrease resources of cognitive processing and vice versa. However, the arousal-conflict interaction and the modulation of emotional arousal found within the dACC during the late negativity stage in Study 1, that possibly initiated response conflict resolution immediately discards the aforementioned notion.

Overall, the current results indicate that the existence of a push-pull relationship between the dACC and rvACC in this study could be explained by the modulation of emotional valence, which occurred at an earlier N450 window, initially increasing rvACC activity and the modulation of emotional arousal, initiating response conflict resolution at the late negativity window which significantly increased dACC activity. It is suggested that the push-pull relationship between the dACC and rvACC in this study is further investigated by conducting connectivity analysis between the two ACC subdivisions at the specified valence and arousal related conflict modulation time windows.

6.2 Future directions

Despite the promising results, several questions remain unanswered at present, including the impact of emotional valence and arousal during conflict in patients with other psychiatric disorders. A number of possible future studies using the same experimental set up are apparent. It would be interesting to extend this experiment to patients with other arousal-cognitive disorders (e.g. borderline personality disorder, anxiety) (Dresler et al., 2009; Schnell and Herpertz, 2007; Williams et al., 2004) where aberrant dACC activity is expected to relate with cognitive deficit, or valence-cognitive (e.g. depression) related psychiatric disorders (Burbridge and Barch, 2002; Kanske and Kotz, 2012; Koenigsberg et al., 2009; Niedtfeld et al., 2010; Schulze et al., 2011) where aberrant rvACC activations are expected.

Emotion-cognition interactions gone awry can lead to clinically significant levels of anxiety and depression. However, the mechanisms of emotion-cognition remain mostly speculative. A question of interest concerns decoding the interactions between the dACC and rvACC in cognitive-emotional tasks for a deeper understanding of the nature of human perception and behavior (Bush et al., 2000). It has been suggested that when an emotional stimulus is present in a cognitive task, the interactions of the dACC and the rvACC might be present (Bush et al., 2000; Dolcos and McCarthy, 2006; Hart et al., 2010). In a cognitive-emotional fMRI Flanker task (Kanske and Kotz, 2011a), negative emotion is found to increase functional connectivity between dACC and rvACC in conflict trials. This effect is not found in the neutral condition. There is a definite need to explore this connectivity so as to develop a full picture of dACC and rvACC interrelations and to investigate abnormalities in the interactions in patients suffering from emotion-cognition related disorders. It is suggested that methods such as EEG-fMRI is implemented, where correlations between the ROIs (being too close together) would not be a hindrance.

There is abundant room for further progress in determining the functional and effective connectivity between arousal-cognitive and valence-cognitive networks of the brain. For example, the dACC is found to be connected to the dorsal anterior insula (dAI) and the rvACC is found to be connected to the ventral anterior insula (vAI) in resting state studies (Deen et al., 2011). Similar to the rvACC, the vAI is involved in the processing of emotional valence. Similar to the dACC, the dAI is involved in cognitive processes. Connectivity analysis between these ROIs using Lagged Phase Synchronization (LPS) technique with LORETA is recommended as a future study. Meanwhile, the challenge of exploring possible network dysconnectivity between the dACC (at the late negativity window) and rvACC (at the N450 window) with brain regions such as the amygdala and nucleus accumbens that could not be accessed via EEG in Schizophrenia patients could be undertaken using the EEG-fMRI method.

6.3 On the originality of the dissertation

By addressing the limitations of previous studies, this dissertation provides a first comprehensive investigation of the ERP and neural effects of the emotion-cognition Stroop paradigm that includes the valence and arousal dimensions of emotions. Previously, the emotion-cognition Stroop paradigm has only been tested in the neutral and negative conditions (Chajut et al., 2010b). Only behavioral results have been discussed (Chajut et al., 2010b). The importance and originality of this study is that it explores the time course of the dACC and rvACC activity in the modulations of emotional valence and arousal during conflict. Although a lot of research have been performed to determine the functional role of the subdivisions of the ACC, none has used the current methodology to explore this aspect. This study sheds new light on the N450 valence modulation within the rvACC and late negativity arousal modulation within the dACC that initiated response conflict resolution.

The insights gained from Study 1 might be of assistance to emotion-cognition investigation in patients with psychiatric disorders. Study 2 has been one of the first attempts to thoroughly examine and compare the time courses of the dACC and rvACC activation in HC and SZ subjects in the emotion-cognition Stroop task. This approach is useful in expanding the understanding of valence and arousal related conflict deficiencies experienced by patients with SZ. Several noteworthy contributions were made in Study 2, such as unravelling the differences of the temporal dynamics of the dACC and rvACC activity during emotion-cognition interaction in patients with SZ, establishing arousal dysregulation during conflict within the dACC at the late negativity window and valence aberrant modulation within the rvACC during N450 in SZ subjects.

6.4 Final Remarks

This dissertation sets out to explore a largely ignored question, namely the influence of emotional valence and arousal on cognitive control. The first study identifies the effect of emotions on cognitive control at two separate stages where emotional valence modulates rvACC activity during the earlier N450 window and emotional arousal modulates dACC activity during late negativity at which, arousal and cognition interact to initiate response conflict solution. The relevance of the arousal-cognition interaction is clearly supported by the negative correlation between the dACC activity (modulated by emotional arousal) during late negativity with RT and the ex-Gaussian μ, indicating top-down conflict resolution during this window. The time course activity shows the initial higher peaks of rvACC activity caused by task conflict; i.e. the processing of the valence content of task unrelated word has activated selective attention. The subsequent significant higher dACC activity modulated by emotional arousal during late negativity has engaged attentional resources thus contributing to response conflict resolution.

By addressing limitations of previous behavioral research, the neural activity in the emotion-cognition Stroop task has been investigated. The investigation has culminated in a functional profile of emotional valence and arousal modulation during conflict in the emotion-cognition Stroop task in healthy subjects. Evidence from the study suggest that emotion and cognition processes are interrelated, but valence and arousal related conflict processes are distinct within the dACC and rvACC. These findings might resolve an existing controversy in the literature regarding the integrated and/or distinct roles of the dACC and rvACC during emotion-cognition related tasks.

Further, these empirical findings provide a benchmark for detecting aberrant time course dACC and rvACC activity and abnormalities in the modulations of emotional valence and arousal on cognitive control in patients with SZ in Study 2. It is highly suggested that the experiment is repeated on patients suffering from psychiatric conditions involving aberrant reactions to emotional valence and arousal during conflict, such as patients suffering from anxiety, borderline personality disorder, PTSD and depression, to unveil and understand the neurobiology and neuropsychiatry aspects of emotion-cognition interaction in these patients.

Emotion-cognition relationships and related brain mechanisms are receiving increasing attention in the clinical research literature as a means of understanding diverse types of psychopathology and improving biological and psychological treatments. The second experiment aims to assess the differences in the modulations of emotional valence and arousal during cognitive control in SZ subjects in comparison to HC subjects. One of the more significant findings that has emerged from this study is the hypoactivation within the dACC in the high arousing condition, occurring during late negativity in SZ subjects. The decreased dACC activation is associated with cognitive deficiencies and prominent negative traits in SZ

subjects. Further, at the N450 window, emotional valence modulated the rvACC activity in HC subjects but not in SZ subjects.

Taken together, the results of this study has bridged the gap of previous studies indicating hypoactivation within the dACC and dysregulation of emotional arousal within the dACC in relation to cognitive impairment and negative symptoms in SZ subjects. The N450 dysregulation within the rvACC is speculated to be associated with the aberrant salience assignment to neutral stimuli in line with the DA hypothesis in SZ subjects.

Another contribution of the study has been to provide new insights on the significant slower initial increase and lower peaks of time course activity within the dACC and rvACC in SZ subjects. The findings reported here shed new light on the neural mechanisms underlying the disturbances of SZ subjects in selecting their responses in highly-charged emotional-cognitive situations with increased needs for top-down conflict control. Evidence in the dissertation establishes aberrant emotion-cognition interactions and clearly indicates that these interactions may contribute to psychopathology of SZ.

The dissertation has also allowed the identification of emerging directions and concrete venues for future investigations. New possibilities include extending the study to different fields of study such as mathematics anxiety, social anxiety and communication apprehension, all avenues affecting a majority of the world population. This study anticipates a spark of increased research in the interdisciplinary connections between cognitive neuroscience, psychology, psychiatry and artificial intelligence leading to the development of novel, effective therapies and treatments (e.g. reappraisal techniques, transcranial magnetic stimulation or an IOT device to detect and treat valence and arousal related cognitive deficiencies) jointly aimed at emotional factors and cognitive deficits. This creates crucial implications for future practice in increasing quality of life among people of the society.

7 Summary

English

Background The goal of the present dissertation was to investigate the influence of emotional valence and arousal on cognitive control in healthy subjects and patients with schizophrenia (SZ). The anterior cingulate cortex (ACC) plays a prominent role in this context, with different roles of the dorsal (d)ACC and the rostral-ventral (rv)ACC. Previous studies have documented that emotional valence and arousal are processed in separate brain regions, at different time intervals. However, the time course of the valence and arousal modulation during cognitive control within the dACC and rvACC has yet to be unravelled in emotion-cognition studies. The present study is important because not only does it answer a fundamental question about emotion-cognition interactions, it also extends the understanding of these interactions to the domain of a psychiatric disorder, where dysfunctional emotion-cognition interactions are highly relevant.

Methods 64-channel high density EEG was measured during a modified emotional Stroop task. sLORETA region of interest (ROI) analysis was used to produce the time course of activity within the dACC and rvACC. Two experiments were accomplished in this dissertation. In the first experiment, the reaction time (RT), event related potentials (ERP) and sLORETA ROI activations of n = 27 healthy subjects were assessed in all emotional (valence – neutral, positive, negative; and arousal – high, low) and cognitive (congruent, incongruent) conditions. In the second experiment, the RT, ERP and sLORETA ROI activations of n = 20 patients with SZ and n = 20 matched healthy controls (HC) were compared and evaluated in relation to SZ symptoms.

Results In the first experiment, the temporal activations within the dACC and rvACC were strikingly different with more pronounced initial responses in the rvACC and subsequent significant increased dACC activity at the late negativity window. This study identified the modulation of emotional valence at the N450 stage with higher activations in the positive condition within the rvACC. Emotional arousal modulated the late negativity stage; firstly in the significant arousal × congruence ERP effect and in the significant higher current density in the low arousal condition within the dACC. In the second experiment, evidence is presented which shows significant slower initial increase and lower peaks of temporal activity within the dACC and rvACC in SZ subjects. At the late negativity window, the dACC activity was negatively correlated with the significant higher RT in the high arousal conflict condition in the patient group. The findings also indicated that in contrast to the HC group, there was no significant valence modulation effect (non-significant ERP and rvACC ROI) in SZ subjects at the N450 window, due to the higher neural activity in the neutral condition.

Conclusions Using the sLORETA ROI time course analysis, this study has attained a functional profile of the valence and arousal modulation on cognitive control in healthy subjects. Furthermore, underlying disturbances within the dACC during arousal modulation, associated with cognitive deficits and within the rvACC during valence modulation on cognitive control in SZ subjects were unravelled.

German

Hintergrund Das Ziel der vorliegenden Dissertation war die Untersuchung des Einflusses von emotionaler Valenz und Erregung auf die kognitive Kontrolle bei Gesunden und Patienten mit Schizophrenie (SZ). In diesem Zusammenhang spielt der anteriore cinguläre Kortex (ACC) eine prominente Rolle, wobei die dorsale (d) ACC und die rostral-ventrale (rv) ACC unterschiedliche Rollen spielen. Frühere Studien haben gezeigt, dass emotionale Valenz und Erregung in getrennten Gehirnregionen in verschiedenen Zeitintervallen verarbeitet werden. Der zeitliche Verlauf der Valenz- und Arousalmodulation während der kognitiven Kontrolle innerhalb des dACC und des rvACC wurde jedoch bisher nicht in Emotions-Kognitionsstudien aufgeklärt. Die vorliegende Studie ist wichtig, weil sie nicht nur eine fundamentale Frage nach Emotions-Kognitions-Interaktionen beantwortet, sondern auch das Verständnis dieser Interaktionen auf den Bereich einer psychiatrischen Störung erweitert, wo dysfunktionale Emotions-Kognitions-Interaktionen hoch relevant sind.

Methoden 64-Kanal-High-Density-EEG wurden während einer modifizierten emotionalen Stroop-Aufgabe gemessen. Die Analyse der sLORETA-Region von Interesse (ROI) wurde verwendet, um den zeitlichen Verlauf der Aktivität innerhalb des dACC und rvACC zu ermitteln. Im Rahmen dieser Dissertation wurden zwei Experimente durchgeführt. Im ersten Experiment wurden die Reaktionszeit (RZ), ereigniskorrelierte Potentiale (EKP) und sLORETA ROI Aktivierungen von n = 27 gesunden Probanden unter allen emotionalen (Valenz - neutral, positiv, negativ und Arousal - hoch, niedrig) und kognitiven (kongruent, inkongruent) Bedingungen erhoben. Im zweiten Experiment wurden die RZ, ERP und

sLORETA ROI Aktivierungen von n = 20 Patienten mit SZ und n = 20 übereinstimmenden gesunden Kontrollen (HC) verglichen und in Bezug auf Schizophreniesymptome ausgewertet.

Ergebnisse Im ersten Experiment waren die zeitlichen Aktivierungen innerhalb der dACC und rvACC auffallend unterschiedlich mit ausgeprägteren Anfangsantworten in der rvACC und einer anschließenden signifikant erhöhten dACC Aktivität im späten Negativitätsfenster. Diese Studie identifizierte die Modulation der emotionalen Valenz im N450-Stadium mit höheren Aktivierungen im positiven Zustand innerhalb des rvACC. Emotionale Erregung modulierte die Spätnegativitätsstufe; zuerst in dem signifikanten Erregungskongruenz-ERP-Effekt und in der signifikant höheren Stromdichte in dem niedrigen Erregungszustand innerhalb des dACC. Im zweiten Experiment zeigen die Resultate einen signifikant langsameren anfänglichen Anstieg und niedrigere Spitzen der zeitlichen Aktivität innerhalb der dACC und rvACC in den SZ-Probanden. Im späten Negativitätsfenster korrelierte die dACC-Aktivität negativ mit der signifikant höheren RZ im Hocherregungskonflikt in den SZ-Probanden. Die Ergebnisse zeigten auch, dass im Gegensatz zur HC-Gruppe bei SZ-Probanden am N450-Fenster aufgrund der höheren neuralen Aktivität im neutralen Zustand kein signifikanter Valenzmodulations-Effekt (nicht-signifikante ERP und rvACC ROI) auftrat.

Schlussfolgerungen Mit der sLORETA ROI Zeitverlaufsanalyse konnte in dieser Studie ein funktionales Profil der Valenz- und Arousalmodulation der kognitiven Kontrolle bei gesunden Probanden erstellt werden. Darüber hinaus wurden die zugrundeliegenden Störungen innerhalb des dACC während der Arousalmodulation, assoziiert mit kognitiven Defiziten und innerhalb des rvACC während der Valenzmodulation der kognitiven Kontrolle bei SZ Probanden aufgeklärt.

List of abbreviations

µ : mu

µV : microVolt

ACC : Anterior Cingulate Cortex

ADHD : Attention Deficit Hyperactivity Disorder

Ag/AgCl : Silver/silver chloride reference electrode

ANOVA : Analysis of Variance

BA : Brodmann Area

BAWL-R : Berlin Affective Word List Reloaded

CPU : Central Processing Unit

DA : Dopamine

dACC : Dorsal Anterior Cingulate Cortex

EEG: Electroencephalogram

EOG : Electrooculogram

ERP : Event-Related Potential

f : female

fMRI : Functional Magnetic Resonance Imaging

GG : Greenhouse-Geisser

HC: Healthy Control

HPA: Hypothalamic Pituitary Adrenal

Hz : Hertz

IOT : Internet of Things

kΩ : kiloOhm

LANG : Leipzig Affective Norms for German

ln : Natural log

LORETA : Low Resolution Electromagnetic Tomography

LPC : Late Positive Component

m : male

ms : milliseconds

PANSS : Positive and Negative Syndrome Scale

PET : Positron Emission Tomography

PTSD : Post-Traumatic Stress Disorder

ROI : Region of Interest

RT : Reaction Time

rvACC : Rostral-Ventral Anterior Cingulate Cortex

SE : standard error

sLORETA: standardized LORETA

SZ : Schizophrenia

Sz: Patients with Schizophrenia

σ : sigma

τ : tau

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11 Curriculum Vitae

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Appendix

Appendix 1. Table of means (and standard deviations) of self-reported ratings of valence and arousal and example of stimuli for each emotional condition for LANG (top) and BAWL-R (bottom).

	Valence Rating (mean ± SD)	Arousal Rating (mean ± SD)	Example of words
Low Arousal Neutral	5.02 ± 0.67	1.80 ± 1.58	cup, flour
	0.17 ± 0.84	1.79 ± 0.94	cap, number
High Arousal Neutral	4.98 ± 1.51	4.10 ± 2.40	needle, organ
	-0.005 ± 1.32	4.06 ± 0.90	storm, spicy
Low Arousal Positive	6.26 ± 2.05	3.74 ± 2.39	rest, flower
	1.98 ± 0.77	1.47 ± 0.74	sleep, peace
High Arousal Positive	7.02 ± 2.62	7.20 ± 2.17	love, wonder
	1.96 ± 0.75	3.96 ± 0.89	win, triumph
Low Arousal Negative	3.68 ± 1.98	3.98 ± 2.31	cough, mites
	-1.9 ± 0.74	2.58 ± 1.24	alone, weak
High Arousal Negative	2.79 ± 2.69	7.33 ± 2.15	rage, terror
	-2.36 ± 0.84	4.32 ± 0.92	death, fear

A total of fifty two words were selected from LANG (Kanske and Kotz, 2010) as emotional stimuli in this study. Words in LANG are rated with regard to valence and arousal

using nine-point rating scales. In BAWL-R (Võ et al., 2009) emotional valence is rated on a 7-point scale and arousal on a 5-point scale. A total of forty-four words were selected from BAWL-R as emotional stimuli in this study.

The words from BAWL-R were transformed to a 9-point scale similar to LANG using linear transformation. A 2×2 factorial ANOVA (valence × arousal) conducted in STATISTICA revealed a significant main effect of valence [$F(4,178) = 168.57,\ \text{partial}\ \eta^2 = 0.7911,\ p < .01$]. Bonferroni-*t* post-hoc tests revealed positive words were more pleasant than neutral ($t(62) = 16.3894, p < .01$) and negative words ($t(62) = 25.5331, p < .01$) while negative words were more unpleasant than neutral words ($t(62) = -17.1540, p < .01$).

Arousal ratings were significantly higher for high compared to low arousal words [$F(2,89) = 205.059,\ \text{partial}\ \eta^2 = 0.8217,\ p < .01$].

12 Affidavit – Statutory Declaration

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.

Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.

Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Hamburg, den 25.06.2018 Farah Shahnaz Binti Feroz