Cognitive/Neural Compensatory Mechanisms in Schizophrenia: Reaction Times-Brain Activity Correlates

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Dedication

I dedicate the current work to Egypt, my home and land of Pharaohs country. Hopefully, I have been able to plant a seed in a shining future. I also dedicate it to my parents, my sisters and my kids. Just being in my life makes it meaningful.

Abstract

Cognitive deficiency in schizophrenia (SZ) was found to be associated with decreased PFC activity compared to healthy controls (HC). Other studies referred to increased / intact patterns of PFC activity. Parallel to those inconsistent neuroimaging findings, schizophrenia patients also showed increased intra-individual reaction times variability (RT_IIV). In the current work, we suggested that inconsistent findings in schizophrenia neuroimaging literature are driven by their increased RT-IIV. We hypothesized that performance with increased reaction times in SZ patients reflects compensatory cognitive/neural mechanisms. To address that general hypothesis, we conducted three studies as follow: 1. Activation likelihood Estimation (ALE) meta analysis of (90 fMRI studies in SZ); In that study we were first concerned with extracting the most consistent neuroimaging findings in the previous SZ literature. Second, we conducted ALE analyses within two categories: experiment with impaired RT (effect sizes > 0.3) vs. experiments with unimpaired RT (effect sizes <0.3); 2. In the second study, we investigated RT_IIV coefficients during AX task performance in four groups, SZ patients (N= 20), SZ.R (N= 33), HC subjects (N =21), HC.R (N= 23). We hypothesized that SZ patients and their relatives would show increased RT_IIV relative to HC within the probe and the cue conditions. 3. In our main study, fMRI study, we tested BOLD response across three levels of RT (slow, medium and fast). We hypothesized that SZ patients and their relatives will show more VLPFC activity during the slow trials than the faster trials relative to HC- reflecting slow reactive compensatory mechanisms.

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Chapter 1 Review and Background on Cognitive performance for Schizophrenia

Foreword: *This chapter was written in collaboration with Angus W. MacDonald who edited and revised versions of the manuscript.*

Introduction.

Worldwide, schizophrenia is one of the most prevalent serious and persistent mental disorders. The most common clinical features in schizophrenia (SZ) are psychotic symptoms including auditory hallucinations, paranoid or bizarre delusions, and disorganized speech and thinking. Patients also commonly suffer significant social or occupational dysfunctions, poor emotional responsiveness, thought disturbances (Tandon et al., 2013; Tandon, Nasrallah, & Keshavan, 2009), as well as psychomotor disturbances such as general slowness (Morrens, Hulstijn, & Sabbe, 2007; Ngan & Liddle, 2000; Peralta, Campos, De Jalón, & Cuesta, 2010). Numerous studies have emphasized that cognitive impairment is an important correlate and determinant of these disturbances in SZ, perhaps even more important than psychotic symptoms themselves (Dickinson, Ragland, Gold, & Gur, 2008, Keefe et al., 2007a,b). At the same time, it has been difficult to understand the nature of this impairment and the neural alterations underlying it. The current paper adopts an integrative approach for understanding this impairment as well as compensatory neural and cognitive mechanisms in SZ. I argue that performance variability in SZ reflected by their reaction times (RT) for accurate and inaccurate trials, in particular a metric known as reaction times intra-individual variability (RT-IIV) (Kaiser et al., 2008; Rentrop et al., 2010; Vinogradov, Poole, Willis-Shore, Ober, &

Shenaut, 1998), may provide insight into SZ patients' neural and cognitive efficient and inefficient compensatory mechanisms.

As an introduction to this thesis, this chapter will review cognitive impairments in SZ in the previous literature. I will discuss the well-known hypothesis of context processing deficiency as a core deficit that affects the other cognitive domains (Barch et al., 2004; Cohen et al., 1992; Holmes et al., 2005; MacDonald & Carter, 2003). Then, I will discuss the Dual Mechanisms Control Theory demonstrating the neural and behavioral characteristics of proactive and reactive control mechanisms that dealing with the context information. More specifically, the current chapter reviews the direct evidence on the proactive control deficiency in SZ groups. This will be followed by an overview of the functional neuroimaging findings in SZ focusing on the inconsistency of these findings. Performance and functional heterogeneity will be discussed as a proposed reason for such inconsistent findings. In the section after, I will show the evidence of the heterogeneous or unstable cognitive performance - reflected by the increased reaction time variability - in SZ. I will discuss the general slowness in SZ as behavioral evidence on proactive control deficiency followed by a review of the previous findings on RT-IIV in SZ as behavioral evidence on adopting other compensatory mechanisms. The next section will discuss the neural alterations associated with the increased intra-individual reactions times in healthy and SZ patients. Finally, the chapter will suggest hypothetical proactive and reactive mechanisms in SZ relying on the different patterns of brain activity-performance correlates that form the theoretic basis of this dissertation. Discussing different approaches of testing brain activity-RT relationships will follow this

highlighting the utility in investigating neural correlates to trial-by-trial RT analysis in SZ.

Background: Inconsistencies and Instability in The Clinical Cognitive Neuroscience of Schizophrenia.

Strong debates have continued about whether they are independent specific cognitive deficits, a cognitive factor that mediates the other cognitive functions (e.g. context processing, encoding, processing speed), or a general factor that mediates cognitive functions (Barch, 2006; Dickinson, Iannone, Wilk, & Gold, 2004; Green & Harvey, 2014). Parallel neuroimaging studies focused on identifying the associated neural alterations during the cognitive performance. They have been mainly concerned with the differences and the similarity of the neural alterations in SZ across different cognitive domains (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009; Kindermann, Karimi, Symonds, Brown, & Jeste, 1997). The main aim was to Fig. out if the specific neural mechanisms that underlie some or all-cognitive dysfunctions are core pathological factors in SZ.

Unfortunately, neuroimaging findings have been inconsistent. Although most studies reported decreased activation in PFC area (e.g. Barch et al., 2001; Perlstein, Dixit, Carter, Noll, & Cohen, 2003), other studies found this area to be equally or increasingly activated in individuals with SZ (e.g. Callicott et al., 2000; Manoach, 2003). Besides, other findings of cortical and subcortical hyperactivations found to be associated with the decreased frontal lobe activity. The findings of hyperactivations have been explained as compensatory mechanisms that SZ patients adopt to compensate for their cognitive

impairment (Minzenberg et al., 2009; Glahn et al., 2005).

Likewise, although there is considerable evidence on the cognitive impairments in SZ, cognitive performance instability was characteristic for SZ patients. Previous studies found increased intra-individual as well as intra-group reaction time variability in SZ patients when they compared to HC (Kaiser et al., 2008; Vinogradov et al., 1998).

While RT intra-individual "across trials" and intra-group "across subjects" variability, as well as fMRI inconsistent and variable findings, show the possibility that SZ patients adopt different mechanisms through the same cognitive task, few studies were concerned with investigating the behavioral and neural characteristics of these mechanisms. Linking both variables "behavioral performance" / "brain activity" together may potentially help understand the cognitive disturbances and the compensatory mechanisms that account for these fluctuating findings in SZ literature. Since, it is intuitive that behavioral fluctuations is associated with neural alterations, investigating different patterns of behavioral performance across trials instead of averaging it for each subject would solve - in part - the inconsistency reported in fMRI studies. That approach of analysis helps to understand the neural mechanisms associated with each pattern of cognitive response and whether its proactive or reactive control depending on the RT and neural alterations as assumed by the Dual Mechanisms Control theory (Braver, 2012).

The following few pages show a brief summary of cognitive disturbances in SZ and shed light on the context processing as a core factor for a wide range of these disturbances. I will discuss the Dual Mechanisms of Control (DMC) theory introducing the proactive and reactive mechanisms as explanatory strategies of the context

processing. By the end of this section, I will review previous findings of proactive and reactive control in SZ.

Cognitive Disturbances in Schizophrenia- Specific Deficits vs. General Impairments.

In a huge literature, there has been a great interest in the cognitive impairments in SZ. Cognitive dysfunction was a strong predictor for the outcome in SZ. Numerous studies illustrated that cognitive impairment is an important correlate and determinant of functioning in SZ, perhaps even more important than psychotic symptoms (Dickinson, Ragland, Gold, & Gur, 2008, Keefe et al., 2007a,b), with the poorest cognitive function associated with the poorest social and occupational outcomes and the least ability for remediation (Green, 1996; MacDonald & Carter, 2002). It has been argued that some of the cognitive deficits reflect more fundamental features of the illness and perhaps reveal vulnerability factors for SZ when compared to other biological and physiological findings. The review study for Heinrichs et al (2005) reported that the average effect sizes of common clinical tests of attention, language, memory, and reasoning was twice as large as those obtained in MRI and PET (Heinrichs, 2005).

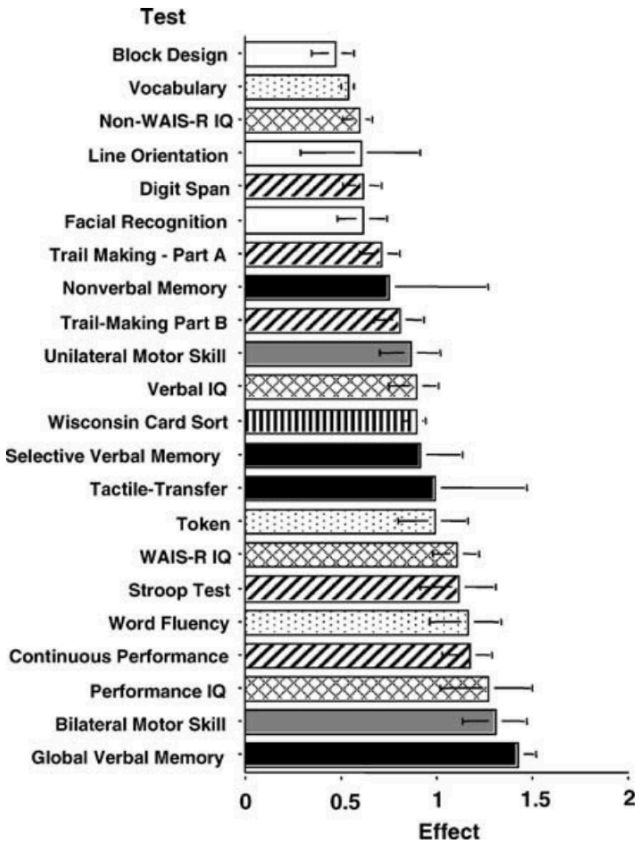


Fig. 1-1 *Heinrich et al. (1998). Means and SE for effect sizes of different cognitive tasks in SZ.*

Although previous literature in SZ hypothesized that SZ patients have impairments in independent specific cognitive domains while other functions are intact, a growing evidence illustrated that across different cognitive domains, including attention, working memory, verbal and visual memory, verbal and visual learning, reasoning and problem solving, and processing speed SZ patients show significant disturbances comparing to healthy controls (Carter et al., 2010; Lee & Park, 2005; MacDonald & Carter, 2003). In one early large meta-analysis, Heinrichs et al (1998) estimated 22 mean effect sizes from 204 studies that investigated global and selective verbal memory in SZ

versus HC, nonverbal memory, bilateral and unilateral motor performance, visual and auditory attention, general intelligence, spatial ability, executive function, language, and inter-hemispheric tactile-transfer test performance. The authors found that SZ is characterized by a broadly-based cognitive impairment, with varying degrees of deficit in all behavioral domains measured by standard clinical tests (Fig. 1-1, Heinrichs & Zakzanis, 1998). The authors suggested that many cognitive tasks are sensitive to SZ simply because they are effort demanding rather than because they require mental operations selectively impaired in the illness. These considerations are complemented by the likelihood that the processing requirements of a cognitive task interact with impaired brain systems to influence discriminating power and effect sizes. Thus, if defects in specific cerebral systems underlie SZ, then tasks mediated by those systems will be impaired. In addition, it was also found that cognitive disturbances in SZ are mediated with one factor. Dickinson (2004), supported that a generalized cognitive deficit is a core feature of SZ. The authors used a specialized structural equation modeling approach, single common factor analysis, to investigate the generalized versus independent cognitive deficits in SZ. They analyzed eighteen scores from the Wechsler Adult Intelligence Scale-III and the Wechsler Memory Scale-III. About two-thirds of the overall effect of the illness on cognitive performance was mediated through one factor. The Wechsler subtest scores showed strong relationships with this factor. The independent associations of group status with the subtest scores were smaller in magnitude and only selectively significant. Based on these findings, the authors concluded that the relatively greater magnitude of illness effects mediated through the

common factor, compared with the specific, independent effects (Dickinson et al., 2004).

In a second study concerned with the cognitive domains, Dickenson et al. (2008) found that SZ cognitive deficit is largely generalized across all domains, with small effects of the illness on selected domains. The author applied seventeen neuropsychological variables in 148 SZ patients and 157 HC. The variables were grouped into six familiar cognitive domains and linked these to a higher-order, general cognitive ability factor. About 63.6% of the diagnosis-related variance in cognitive performance was mediated through a generalized factor, with smaller direct effects on each domain, verbal memory and processing speed (Dickinson et al., 2008).

Recently, there is a strong trend to re-conceptualize the range of deficits in SZ as reflecting a "generalized" cognitive impairment, assuming that cognitive impairments across domains share the same neurobiological source (Barch & Sheffeild, 2014). One mechanism suggested to affect broadly other cognitive functions in SZ is the context-processing deficiency. According to this approach, SZ patients have difficulty to actively represent goal information to guide them through a cognitive task performance. This pattern of deficiency are thought to be associated with decreased activity in Dorsolateral Prefrontal Cortex (Barch & Sheffeild, 2014)

Context Processing Underlying Cognitive Impairments.

Cohen et al. (1992) was the first to suggest that the context processing deficiency is responsible for range of cognitive deficits in SZ patients. (Barch et al., 2001; Braver et al., 1999; Braver & Cohen, 1999; Cohen et al., 1999; Cohen & Servan-Schreiber, 1992). In previous study, Cohen et al (2008) suggested that intact function of dopamine in

DLPFC was responsible for the context processing, and that a disturbance in this mechanism was responsible for a range of cognitive deficits in SZ. Context processing refers to prior task-relevant information, including the instructions, goals that are represented and maintained in working memory and the results of processing prior stimuli. Deficits in working memory, attention, inhibition and language processing in SZ can arguably be understood in terms of a deficit in context- processing. Each of these domains requires the active representation of such context information for effective function. It is well known that context processing and working memory are not completely independent constructs. However, the context-processing hypothesis states that the failure of maintenance and manipulation of the contextual information elicits deficits among SZ patients (Barch et al., 2004). Numerous prior studies have provided support for these hypotheses concerning context-processing deficits in SZ, along with evidence for context processing disturbances in individuals at risk for SZ (MacDonald & Carter, 2003; MacDonald, Pogue-Geile, Johnson, & Carter, 2003; Poppe, Carter, Minzenberg, & MacDonald, 2015). Generally, regions involved in context processing include the lateral PFC, the anterior cingulate cortex (ACC), basal ganglia and brainstem systems. However, the specific functions of these regions and their role in the cognitive process still unknown.

In real life as well as cognitive tasks, different situations drive different pattern of context processing tradeoffs. For example for "goal representations" -- depending on the situation -- subjects may chose to maintain the same goal information before the beginning of the task to its end, while in other situations with unexpected changes

subjects may chose to reactivate the goal information with each change and for each trial. Also the "attentional commitments", the situations that require subjects to maintain goal information make cognitive process more closed and less sensitive to unexpected changes "bottom up stimulus". On the other hand, other situations are stimulus dependent and transient. They do not dependent on previous contextual information, instead they rely more on strong unexpected "bottom up" cues to restore goals for each trial (Braver, 2012; Irlbacher, Kraft, Kehrer, & Brandt, 2014). In addition to these situational factors, other individual factors may also influence the value estimates of the relative benefits and disadvantages of a certain strategy, e.g. memory capacity, rewards sensitivity, motivation, etc., (Irlbacher et al., 2014).

According to the factors mentioned above, subjects may have different mechanisms dealing with the context information. In the dual mechanisms of control (DMC) theory, Braver and co-workers have suggested two different but complementary control modes, referred to as proactive and reactive mechanisms (Braver, 2012; Marklund & Persson, 2012). In the next few pages, I will be discussing both mechanisms focusing on their cognitive role, neural associations integrative function, and their behavioral performance differences. Then I will discuss the theoretical assumption of intra-individual performance variability explained by the DMC mechanisms.

Proactive Vs. Reactive Cognitive Control (Dual Mechanisms of Control Theory-DMC)

Recently, the key role of context processing in SZ has been re-conceptualized more broadly as the function of proactive cognitive control (Barch & Ceaser 2012), or in other words, the ability to "proactively" maintain the goal-related information that can be

used to guide behavior. The proactive control mode is an early selection, when subjects actively maintain the goal-relevant information in a sustained or anticipatory manner, even before the occurrence of cognitively demanding events. This in turn allows for directing the attention, perception, and action systems in a goal-driven manner. In contrast, in the reactive control is recruited as a ‘‘late correction" mechanism that is utilized only when needed, after a high-interference event is detected. Thus, the proactive control relies on the anticipation of interference before it occurs, whereas reactive control relies on the detection of interference after its onset (Barch & Sheffeild, 2014; Braver, 2012).

From a behavioral view, an influential model of cognitive control suggests that it can work on different time scales (Irlbacher et al., 2014). A proactive mechanism “earlier selection” would take lower RT compared to a reactive, “on-the- fly” response (Barch & Ceaser, 2012; Braver, 2012). For the proactive strategy, the subjects start each trial with a processed context information ready to be used, while for the reactive strategy, the subjects start each trial by reprocessing the context information consuming more time. In a recent review, Irlbarcher et al. (2014), referred to two forms of the reactive mechanisms in the literature, late and early reactive mechanism. The authors suggested that the early reactive mechanism is slower than the proactive mechanisms and faster than the late reactive mechanism.

The Dual Mechanisms of Control theory provides a strong prediction about the temporal dynamics and location of brain activity under proactive versus reactive control. From a neural view, Proactive control should be associated with sustained and/or

anticipatory activation of the lateral PFC, which reflects the active maintenance of task goals due to its connectivity with sensorimotor regions. This goal maintenance activity serves as a source of top-down control that can facilitate the processing of expected an upcoming event that has a high cognitive demand. A successful proactive mechanism should be associated with increased DLPFC activity during the cognitive performance. Proactive control depends more on the ability to mount a sustained pattern of neural activity, a well-characterized aspect of the prefrontal cortex that is observed during both physiological recording in non-human primates (Braver, 2012).

By contrast, reactive control is more likely to be reflected in a transient activation of lateral PFC, as well as a wider network of additional brain regions. This activity might reflect the bottom-up reactivation of task goals. It should be mediated either via associative and episodic associations (e.g. posterior cortical or medial temporal lobe regions) or via the detection of interference through activating conflict monitoring regions (e.g. anterior cingulate cortex ACC); That should be associated with detecting conflict and recruiting DLPFC engagement on a trial-to-trial basis (Braver, 2012). The DMC theory proposes that the ACC plays a role in the proactive as well as the reactive control networks. Others, suggest a dichotomy of medial frontal regions (pre-supplementary motor area (pre-SMA) and ACC) in the sense that ACC is involved in reactive control, whereas pre-SMA is activated in proactive cognitive control, regardless of the level of information processing at which conflict occurs (Irlbacher et al., 2014).

In addition, both mechanisms should differ in terms of dopaminergic (DA) system functioning. The ability to actively sustain inputs in PFC requires a phasic DA-mediated

gating signal occurring at the time when contextual cues are presented. PFC can only be transiently activated without such a gating signal (Braver, 2012).

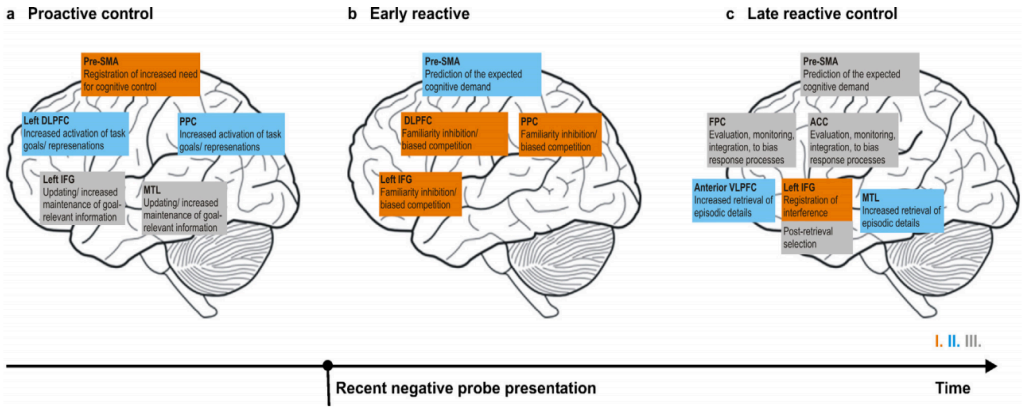


Fig. 1-2 *Irlbacher et al. (2014) Time course of proactive and early/delayed reactive mechanisms - neural and time proposed characteristics.*

According to this theory, successful cognitive function depends on both proactive and reactive strategies. The two mechanisms are not fully independent. It is likely to be some bias favoring one of them over the other. Adopting proactive or reactive mechanisms or shifting between both mechanisms depend on the task situation and may also be characteristics of the individual. The central aspect of the Dual Mechanisms Control Theory provides a framework for understanding the intra-individual and inter-individual variability in cognitive control function. It also provides an explanation for the changes in cognitive control that may be present in different populations (Braver, 2012).

According to The Dual Mechanisms Control Theory, the differences between

proactive and reactive control mechanisms are important for understanding the inter-group, intra-group, inter-individual and intra-individual performance variability. An alteration of situational or individual factors should result in alteration of adopting proactive and reactive control strategies. For example, when expectancy is high, proactive control is recruited instead of reactive control. In Burgess and Braver 2009 study, the authors focused on shifts in cognitive control mechanisms for dealing with anticipated/ not anticipated interference during working memory. Participants performed a probes task under different level of interference expectancy. In the low level of expectancy, recent negative probes occurred only rarely, whereas in the high expectancy condition they were frequent. The authors assumed that expectancy manipulation led to a shift in the temporal dynamics of lateral PFC activation specifically, in accordance with predictions of the DMC Theory. Replicating prior findings, Burgess and Braver found that left inferior PFC - as well as other medial and lateral PFC regions - showed a probe-triggered hyperactivation, consistent with manipulation of reactive control. By contrast, in the high level of expectancy, lateral PFC activity increased during the delay period, prior to probe onset (Braver, 2012).

Proactive / Reactive Control in Schizophrenia.

Although a huge amount of literature focused on cognitive deficiency in SZ, and the neural mechanisms behind, a few studies were concerned with investing the nature of the cognitive control deficiency and whether its reactive and proactive control problem. In an early study for Edwards et al (2010), the authors used A-CPT to investigate proactive (cue condition) vs. reactive (probe condition) mechanisms in SZ patients.

Patient with SZ exhibited more brain activation during the probe condition (reactive), while HC subjects showed increased PFC activation during the cue condition.

Zandbelt et al. (2011), presented similar findings when assess proactive inhibition as the effect of stop-signal probability on go-signal response time in SZ patients vs. HC. Two forms of cognitive control were investigated: proactive control (anticipated stops) vs. reactive control (non-anticipated stops). Response time increased as a function of stop-signal probability in SZ patients relative to HC, with siblings performing at an intermediate level. Proactive inhibition was impaired in SZ patients and their siblings relative to HC. That impairment was associated with decreased activity in right striatum, inferior frontal cortex, and bilateral temporoparietal conjuction. Groups showed no differences during reactive control condition (Zandbelt, van Buuren, Kahn, & Vink, 2011).

Recent study utilized the color word Stroop task and (AX-CPT) to test reactive and proactive control processes, respectively in SZ patients vs. HC. The authors contrasted cueA to cueB (B-A) of AX-CPT task for a proactive control, and incongruent trials to congruent trials (I-C) of Stroop test for reactive control. HC subjects were found to demonstrate DLPF , ACC, and parietal cortex activity on both tasks. On the other hand, while SZ patients showed activation similar to HC subjects during reactive control, they did not show any significant activation during proactive control. HC subjects exhibited more activity in DLPFC and IPL for (proactive control-reactive controls) contrast relative to SZ patients (Lesh et al., 2013). Using DPX task - an edited version of AX-CPT- task (Poppe et al., (2016) found that HC subjects displayed significantly more

activation in the right and the left MFG masks for B-A contrast, while groups did not differ significantly in the right IFG mask (Poppe et al., 2016).

As shown above, there is growing evidence that SZ patients have proactive control deficiency associated mainly with reduced brain activity in PFC. It was also suggested that proactive control deficiency is also characteristic of people with high risk to SZ (Zandbelt et al., 2011). To this end, it is important to understand how these findings are consistent with previous findings of cognitive performance and its neural associations in SZ. According to the proactive deficiency hypothesis in SZ, SZ patients are expected to exhibit reduced prefrontal activity in the (DLPFC), decreased accuracy as well as increased RT during cognitive tasks. Neither neuroimaging studies nor behavioral studies confirmed these expectations consistently. 1. Although, previous neuroimaging findings demonstrated reduced PFC activity in SZ during the cognitive performance, other studies found it to be equally or increasingly activated (Callicott et al., 2000; Manoach, 2003). Other findings also demonstrated other patterns of hyper and hypoactivation (see next section). 2. In addition, SZ patients show increased reaction times intra-individual variability (RT-IIV) in comparison to HC. While, this may reflect proactive deficiency it also reflect unstable reactive responses. I'll be discussing the fluctuating neural and behavioral findings in detail in the next two sections.

Brain Activity Alterations Associated With Cognitive Performance In Schizophrenia: Inconsistency and variability.

According to Green et al. (2013), neuroscientific methods can help understanding the nature of the cognitive impairment. For example, ceiling and floor effects, which are

one source of erroneous conclusions about a differential deficit with behavioral measures, have less effect on physiological methods. A behavioral ceiling effect reflects the limit of a measurement system, while a physiological ceiling effect reflects the limit of a biological system. The generalized deficit problem means that a generalized deficit gives the false appearance of a differential deficit, not when ceiling or floor effects represent a biological reality. Because fMRI can reveal qualitative patterns on multiple dimensions, it provides ways to determine whether results are consistent with a unidimensional-generalized deficit. Groups may differ in brain regions activated during a certain task performance, or they may differ qualitatively when the difficulty of a task is parametrically manipulated. Regional measurement typically involves patterns of responses that are multidimensional or nonlinear, such as the inverse-U response seen with working memory tasks. Alterations of brain activation between groups at similar levels of performance may reflect different cognitive mechanisms participants adopt on a task to achieve a level of competence. Subjects may rely on compensatory alternative brain regions to achieve a level of performance. They can also differ in how efficiently they perform a task at different levels, e.g. in the number of voxels recruited. (Green, Horan, & Sugar, 2013)

The following is a review of brain imaging studies concerned with brain activity alterations during the cognitive performance. For the first part, I will review the findings from meta-analysis studies. Then, I will discuss the inconsistency of the findings supported by single studies. At the end of this section, I will discuss the proposed reasons for the inconsistent findings focusing on heterogeneity and variability within and between

SZ groups.

Functional Neuroimaging Findings In Schizophrenia.

Evidence of hypoactivation. Supporting the proactive deficiency hypothesis in SZ, large literature found SZ patients to have a decreased brain activity compared to HC subjects in relevant brain regions (Braver, 2012; Barch & Ceaser, 2012). In very early research, Ingvar and Franzen (1974) found individuals with SZ to have a pattern of " hypofrontality" during rest state. In most of the earlier studies using the Wisconsin Card Sorting task, as well as in a number of the more recent studies using tasks such as the N-back and mental arithmetic, the modal finding has been of decreased activation in DLPFC in SZ (Barch, Csernansky, Conturo, & Snyder, 2002; J H Callicott et al., 1998; C. S. Carter et al., 1998; Jansma, Ramsey, Van der Wee, & Kahn, 2004; Mendrek et al., 2004; Perlstein, Carter, Noll, & Cohen, 2001). In fact, Davidson and Heinrich (2005), found the largest average difference between SZ patients and HC subjects derives from frontal lobe physiology during cognitive tasks. Hypofrontality was the most replicated findings in SZ. In particular, fMRI studies found considerable evidence that SZ patients fail to activate the dorsolateral prefrontal cortex (DLPFC) as much as normal comparison subjects during working memory or executive task performance(Glahn et al., 2005; Minzenberg et al., 2009).

Evidence of hyperactivation. Although the growing evidence on hypoactivation in general and ''hypofrontality'' in specific in schizophrenic relative to HC, several previous studies have reported equal (Honey, Bullmore, & Sharma, 2002; Hugdahl et al., 2004; Jansma et al., 2004; Kim, Zemon, Saperstein, Butler, & Javitt, 2003; Sandra S

Kindermann, Brown, Zorrilla, Olsen, & Jeste, 2004; Manoach et al., 1999; Walter et al., 2003) or increased prefrontal activity (Callicott et al., 2000; Manoach, 2003; Quintana, Davidson, Kovalik, Marder, & Mazziotta, 2001) that sometimes co-occurred with decreased DLPFC activation in different regions.

Some of these studies found relationship between hyperactivation and task performance. Manoach et al. (1999) suggested that the performance and hyperactivation in SZ patients are manifestations of prefrontal dysfunction reflecting inefficient functioning of the neural circuitry of working memory. The authors tested dorsolateral prefrontal cortex (DLPFC) activation in 12 schizophrenic and 10 normal subjects during their performance of a working memory task. They compared a high working memory load condition with a non-working memory choice RT condition and with a low working memory load condition. Two cognitive tasks were utilized: a modified version of the Sternberg Item Recognition Paradigm, a continuous performance, choice reaction time task that requires working memory. SZ patients performed worse than normal subjects in both tasks. They also showed greater activation in the left DLPFC but did not differ in the right DLPFC or in the control region, while left DLPFC activation was inversely correlated with task performance, as measured by errors. The relation of left DLPFC activation to errors in all three conditions was significantly different for the SZ patients versus the normal group.

Similarly, Callicott et al. (2000) found increased and inefficient cortical activity in SZ patients especially of dorsal PFC. The authors investigated PFC function in SZ using functional magnetic resonance imaging (fMRI) and a parametric version of the n-back

working memory task. SZ patients performed relatively well on this task. The authors pointed out three findings: 1. A greater magnitude of PFC fMRI activation in the context of slightly impaired working memory task performance in SZ. 2. The significant correlations between behavioral working memory performance and dorsal PFC fMRI activation were in opposite directions in the two groups (Callicott et al., 2000).

Other studies show equal DLPFC activation in SZ patients, for example, in Walter et al. (2001) study, the authors examined the cortical activation during a verbal and spatial working memory task (2-back) in SZ. They hypothesized that SZ patients will show hypofrontality in both tasks and decreased lateralization of prefrontal activation. The results showed no significant differences in frontal activation between HC subjects and SZ patients, even at the threshold of $p < 0.01$. (Walter et al., 2003)

Inconsistent findings of neuroimaging cognitive studies in SZ are suggested to be results of different methodological factors such as between groups task performance differences (Callicott et al., 2000), differences in demands of tasks across studies (Barch et al., 2001; Curtis et al., 1999), technical confounds, e.g. head motion (Bullmore et al., 1999) or functional heterogeneity in SZ patients (Manoach, 2003). Reviewing previous studies of hypofrontality during working memory tasks, Manoach et al. (2003) pointed out different reasons for these findings: 1. Artifact Methodologies: Manoach suggested the findings of hypofrontality might be results of an artifact of methodologies that require group averaging and mask possible structural and functional heterogeneity of the DLPFC; 2. Choice of tasks: for example, the authors argue that studies supported hypofrontality hypothesis in working memory mainly employed Wisconsin Card Sort

Test (WCST). The successful performance on WCST depends on sustained attention; concept formation and task switching makes it difficult to utilize an appropriate baseline tasks that isolate WM processes for contrastive neuroimaging analyzes; 3. Measurement issues: reliability and heterogeneity Discrepant.; 4. And finally, performance differences: motivation and capacity, A motivation is a prominent feature of SZ that may represent a possible confound in studies of cognitive performance (Manoach, 2003).

Attempting to reduce the effects of the methodological factors in fMRI single studies in SZ, quantitative reviews of these findings have been presented during the last decade.

Hypoactivation / Hyperactivation in Neuroimaging Reviews.

An early meta-analysis of (MRI) and (PET) studies that examined frontal and temporal lobes activation in 4043 SZ patients and 3977 HC. In this study, Davidson & Heinrichs 2003 used Cohen's d to quantify case-control differences, and moderator variable analysis indexed the relation of sample and imaging characteristics to the magnitude of these differences. In conjunction with cognitive activation tasks, hypofrontality was the strongest evidence demonstrating alterations that distinguish approximately half of SZ patients from HC. Whereas case-control comparisons with structural and functional imaging yield small and unstable findings in some cases (Davidson & Heinrichs, 2003).

Hill et al. (2004), collected voxel-based studies to examine the pattern of prefrontal activation in SZ. Resting and task related frontal activity was both reduced with a medium effect size. The findings supported resting hypofrontality as well as task-

related hypofrontality in SZ (Hill et al., 2004).

Recent meta-analytic studies were concerned with investigating the similarity in blood oxygenation level-dependent (BOLD) response across different cognitive domains using Activation Likelihood Estimation (ALE) technique. ALE is a technique designed to maximize the quantification of inter-study concordance and minimize the subjectivity of the data amalgamation. The ALE technique has three advantages over previous meta-analytic methods: (1) the automation of the analysis, (2) the quantification of the level of concordance in addition to the location, and (3) the use of significance thresholds, providing statistically defensible conclusions. Besides, Instead of labels, foci are the input into the analysis. Labeling of anatomical areas occur after data pooling, and thus is independent of labeling among studies. Finally, foci can be weighted by the number of participants in the studies, giving more validity to the findings (Laird et al., 2011).

In an early application of ALE technique, Glahn et al. (2005) reviewed 12 functional neuroimaging studies that contrasted SZ patients and healthy comparison subjects during the n-back task. The authors found that HC subjects consistently activated bilateral dorsolateral prefrontal cortex, rostral prefrontal cortex, and right ventrolateral/insular cortex more than SZ patients did. While, the left frontal pole, right dorsomedial prefrontal cortex, and anterior cingulate were activated in SZ patients more than they were in HC groups (Fig 3, Glahn et al., 2005).

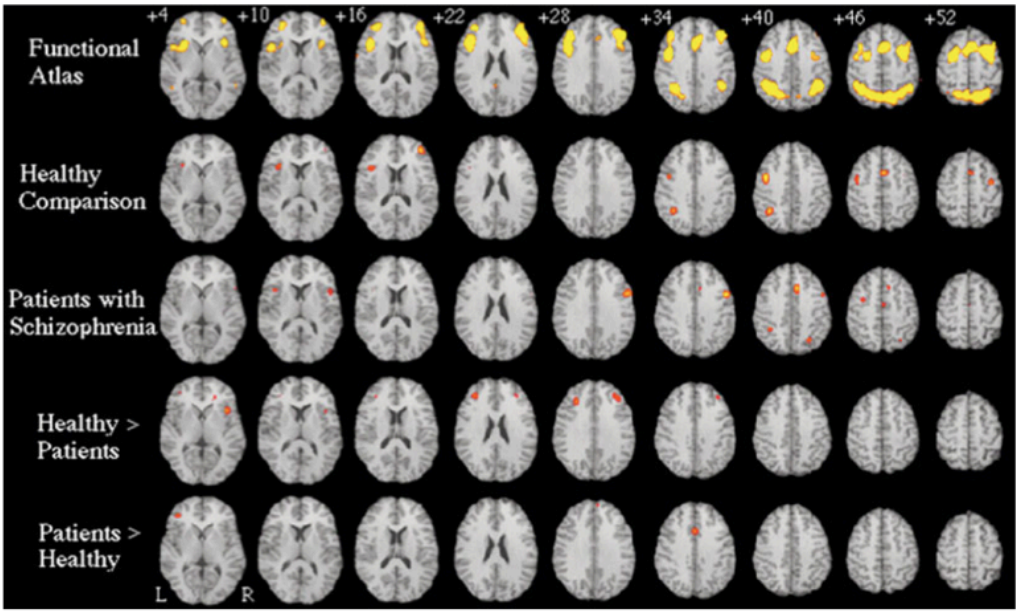


Fig. 1-3 *Glahn et al. 2005. Activation foci reported for healthy comparison, SZ patients, HC > SZ, and SZ > HC.*

A second ALE meta-analysis to take on a similar question contrasted SZ patients and HC subjects during episodic encoding and retrieval (O'Reilly, et al., 2010). 18 whole-brain studies in standard space were included. SZ patients showed less prefrontal activation in the frontal pole, dorsolateral and ventrolateral prefrontal cortex during encoding, and the dorsolateral prefrontal cortex and ventrolateral prefrontal cortex during retrieval. The only medial temporal lobe finding was relatively greater in the SZ patients versus comparison subjects activation in the parahippocampal gyrus during both tasks (O'Reilly, Herd, & Pauli, 2010).

In a broader meta-analysis, Minzenberg et al. (2009) quantitatively reviewed 41 fMRI studies concerned with different cognitive domains. The authors demonstrated that the brain activity of some brain areas of the cortical-subcortical network was significantly

reduced in SZ patients relative to HC. These areas included the bilateral DLPFC, right VLPFC, right ventral premotor cortex, the dorsal CC and a more anterior and inferior area that peaked in the medial frontal gyrus and extended into the ACC. Reduced activity of posterior neocortical areas were also observed in the parietal and occipital cortex. Subcortical areas –included the right putamen and a large area in the left thalamus- were also deactivated in SZ. On the other hand, SZ patients exhibited more activation in the rostral pole of the left PFC and left dorsal and ventral premotor cortex regions relative to HC. A restricted area in the left VLPFC and two midline frontal cortical areas were also hyperactivated. The largest area was located in the dorsal ACC, posterior and dorsal to the ACC area where the SZ patients were impaired, extending primarily into the superjacent SMA.A smaller area was located in the ventromedial PFC. Posterior neocortical areas were found in the temporal and parietal cortex. SZ patients also showed increased activation in Bilateral Subcortical areas – included the insula and amygdala. The authors illustrated two main areas of schizophrenic hypoactivation that co-occurred across the reviewed studies, the first area included the bilateral DLPFC, the right ACC, and the left mediodorsal nucleus of the thalamus. A second area was represented by the bilateral claustrum. Analysis revealed two regions where SZ patients activated more than HC subjects across all studies, including the left ACC and left inferior parietal lobule. As between groups analyses, the ACC sub – region was dorsal and posterior to the ACC subregion, where the SZ patients exhibited impaired activity (Minzenberg et al., 2009a).

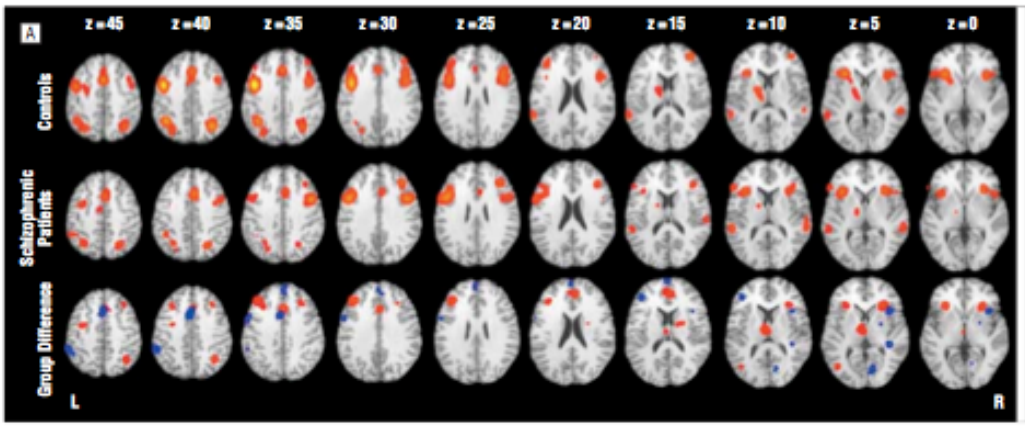


Fig. 1-4 *Minzenberg et al. (2009), Global analysis of executive function studies in SZ;* Global (1st, SZ patients (2nd raw), and group differences – SZ > HC are in red and HC> SZ in blue (3rd raw).

As shown above, a broad network of frontal, subcortical, and posterior brain regions that support task performance were relatively deactivated in schizophrenic SZ patients. For example, the neuroimaging literature review studies showed considerable evidence that SZ patients fail to activate DLPFC as well as ACC relative to HC subjects during cognitive tasks performance. These findings are consistent with the proactive control deficiency in SZ. SZ patients have disrupted frontal-based top-down control functions that lead to a disruption of processing across the distributed brain network supporting task performance (Minzenberg et al., 2009). On contrast, findings of hypoactivation were coupled with inconsistent findings of relatively increased activity in other brain regions that include PFC regions: e.g. left ACC, a midline cortical region located in the ACC extending into the SMA; posterior and inferior cortical areas (Minzenberg et al., 2009; Glahn et al., 2005); medial temporal lobe (O'Reilly et al., 2010); VLPFC; insula and amygdala (Minzenberg et al., 2009a).

While these meta-analytical reviews helped in part in resolving the inconsistency

related to groups' heterogeneity (e.g. ages, medications), tasks (e.g. instructions) and procedures heterogeneity, the findings are still inconsistent for some brain regions. In general, previous studies explained the findings of hyperactivation in SZ as compensatory mechanisms that SZ patients adopt during cognitive tasks to achieve an accurate level of performance. These findings together shed the light on the stability of adopting specific mechanisms between SZ patients as well as across the task "across trials". What follows is evidence on functional and performance heterogeneity in SZ – inter-individual as well as intra-individual variability. I assume that these patterns of heterogeneity contribute in the fMRI inconsistent findings.

In order to average BOLD response across individuals in fMRI studies, it is important to transform brain images into a standardized space (e.g. Talairach or MNI). That transformation requires the stretching and shrinking of the images and may mask individual anatomical and functional differences. For this reason, contrasting findings may be reported from individual statistical maps vs. group-averaged maps. In Manoach et al. (2001) study, the group-averaged findings for SZ vs. HC subjects were consistent with hypofrontality hypothesis (the SZ group activated fewer DLPFC voxels than the HC groups, Manoach et al., 2000). Conversely, the individual subjects data found that SZ patients significantly activated more voxels and showed more activity in DLPFC. Interestingly, it was also found that the activation clusters in HC subjects were about three times more likely to overlap with their averaged group clusters than was the case in the SZ group. The authors concluded that SZ patients were more heterogeneous in their brain activation within the DLPFC. Because of the decreased overlap, averaging the

functional images across subjects may underestimate DLPFC activity in the SZ patients (Manoach, 2001).

Functional variability found to be related to the clinical and cognitive disturbances in SZ. For example, Cole et al. (2011) used resting state functional connectivity magnetic resonance imaging to identify variable dysconnectivity in 23 SZ patients relative to 22 HC. Utilizing a Sternberg task and subtests from the Wechsler Adult Intelligence Scale (WAIS III), the authors examined the cognitive functioning. Dorsolateral prefrontal cortex (PFC) region was identified with global and highly variable disconnectivity involving within-PFC under-connectivity and non-PFC over-connectivity in SZ patients. Variability in this "under/over" pattern of disconnectivity strongly predicted the severity of cognitive disturbances as well as individual differences in every cardinal symptom domain of SZ. It was emphasized the possibility that certain patterns of disconnectivity with a given network might explain individual differences in symptom presentation in SZ (Cole, Anticevic, Repovs, & Barch, 2011).

Recent evidence suggested a major instability of signal processing in prefrontal cortical microcircuits because of reduced phase- synchronization. Winterer et al. (2004) suggested that increased variability of prefrontal physiological responses may represent a fundamental mechanism underlying frontal lobe deficits in SZ. Increased response variability is thought to result from impaired phase resetting of stimulus-induced dynamic changes of ongoing rhythmic oscillations generated in the apical dendrites of pyramidal neurons. Prefrontal response variability of discrete frequency components was investigated across a broad frequency range (0.5–45.0 Hz) during processing of an

oddball paradigm in SZ SZ patients, their clinically unaffected siblings, and healthy comparison subjects. The prefrontal noise was negatively correlated with working memory performance across all groups. Interestingly, the prefrontal noise possessed trait characteristics were strongly associated with genetic risk for SZ. Frontal lobe-related cognitive function depends on the ability to synchronize cortical pyramidal neurons, which is in part genetically controlled. Increased prefrontal "noise" is an intermediate phenotype related to genetic susceptibility for SZ.

In a following study, Winterer et al. (2006) used functional magnetic resonance imaging (fMRI) to scan SZ patients during a visual two-choice reaction task in order to measure, with higher topographic accuracy, signal stability and its relationship to more traditional measures of activation. Twelve clinically stable SZ patients and 16 matched comparison subjects were evaluated. Event-related BOLD responses were subjected to an analysis of residual noise variance and to independent data dimension independent component analysis in the medial prefrontal cortex. The authors reported increased residual noise variance of the BOLD response that predicted the level of prefrontal activation in SZ patients. A residual noise variance in the left hemisphere was strongly correlated with the psychotic symptoms. Independent component analysis indicated unfocussed pattern of activation in SZ patients (Winterer et al., 2006).

As shown above, there is considerable evidence that SZ patients show functional heterogeneity across subjects (Intra-group variability) as well as across trials (intra-individual variability). This heterogeneity could be explained as a result of external factors (e.g. noise; Tregellas, Smucny, Eichman, & Rojas, 2012) or internal factors (e.g.

motivation). While previous studies controlled for the external factors "or at list had a cue for the associated heterogeneity", the internal factors are still uncontrollable during the task. Both factors may work together during the task leading to different patterns of response and reflecting different cognitive/neural mechanisms. As, it is intuitive that brain functioning leads the behavioral performance, I suggest that solving for behavioral performance heterogeneity (if any) should help – in part – solving the associated functional heterogeneity (Wintrer et al., 2006). Interestingly, unstable cognitive performance has been replicated finding in SZ. In the following section, I will show evidence on the heterogeneous behavioral performance in SZ shedding the light to the heterogeneous behavioral performance across trials reflected by the increased RT variability. I will also discuss previous findings of neural alterations associated with RT variability in healthy and SZ patients.

Cognitive Performance Instability In Schizophrenia: Reaction Time Intra-Individual Variability

Parallel to fMRI inconsistent findings in SZ cognitive performance, behavioral studies reported increased intra-individual and inter-group variability of RT in SZ patients relative to HC subjects(Vinogradov et al., 1998). What follows is a review of the previous literature concerned with the processing speed in SZ. I will then discuss the evidence on the increased RT-IIV in SZ.

General Slowness "Increased Response Times Averages" In Schizophrenia patients And Related Neural Alterations.

Psychomotor deficiencies have been observed since the beginning of the 20th

century in SZ. Kraepelin and Bleuler described the phenomenon of psychomotor slowing in SZ as evidenced (Morrens et al. 2007). Recently, Morrens et al. (2007), defined psychomotor as all activities and symptoms in which, rather than thinking or feeling, movement or action is the principal component. These include planning, programing, while execution of movements play a dominant role. Psychomotor tasks are tests focusing on motor skills but involving more than just muscle contractions (Morrens et al., 2007). Generally, SZ patients were found to have lower level of psychomotor activity when they are compared to HC. Previous studies proposed positive correlation between the low level of motor activity and negative symptoms in SZ. Walther research group have accomplished series of studies supporting the dynamical approach of investigating motor behavior in SZ. In Walther et al. (2009) study, 55 SZ patients were studied with 24-h continuous wrist actigraphy. The authors analyzed the activity level (AL), movement index (MI), and mean duration of uninterrupted immobility periods for wakeful periods. These three parameters were strongly inter-correlated. High PANSS negative syndrome subscale scores predicted low activity levels. Single PANSS items (e.g. suspiciousness, hallucinatory behavior, and emotional withdrawal) contributed largely to the variance in activity level and movement index. Age, gender, medication, and duration of illness had no effect on any of the three parameters. The authors concluded that the objectively measured quantity of movement is related to the clinically assessed negative syndrome in SZ. In contrast, PANSS items related to psychomotor behavior imprecisely reflect real quantitative motor activity (Walther, Koschorke et al. 2009).

In a following study, Walther et al. (2009) examined the relationship between resting state (task free) cerebral blood flow (CBF) and objective motor activity in SZ. The study included 11 SZ patients and 14 HC. All participants underwent magnetic resonance imaging with arterial spin labeling and wrist actigraphy. SZ patients showed reduced activity levels and reduced perfusion of the left para-hippocampal gyrus, left middle temporal gyrus, right thalamus, and right prefrontal cortex. In HC, CBF was correlated with motor activity in the right thalamic ventral anterior nucleus, a key module with in basal ganglia-cortical motor circuits. In contrast, positive correlations of CBF and motor activity were occurred in bilateral prefrontal areas and in the right rostral cingulate motor area in SZ patients but not in HC. The authors suggested that basal ganglia motor control was impaired in SZ. In addition, CBF of cortical areas critical for motor control was associated with volitional motor behavior, which may be a compensatory mechanism for basal ganglia dysfunction (Walther, Federspiel, Horn, Razavi, Wiest, Dierks, Strik, Müller, et al., 2011). In a second study for Walther et al. (2011), the authors tested 19 SZ patients and 24 HC subjects using Diffusion Tensor Imaging (DTI), and actigraphy on the same day. SZ patients had lower activity levels relative to HC. They had a lower frequency of activation values in prefrontal and left temporal clusters. Furthermore, using a general linear model, the authors reported linear negative associations of the frequency of activation and activity level underneath the right supplemental motor area, the right precentral gyrus and posterior cingulate gyrus in SZ patients (Walther, Federspiel, Horn, Razavi, Wiest, Dierks, Strik, & Müller, 2011)

According to the previous findings, SZ patients show decreased level of motor

activity, which is associated with decreased brain activity (BOLD) response in the motor areas including the higher function motor areas SMA. Positive correlations of brain activity and motor activity were shown in bilateral prefrontal areas and in the right rostral cingulate motor area in SZ patients but not in HC. Also, the low motor activity in SZ was correlated to PNASS score of negative symptoms and was not affected by the antipsychotic medications. Although previous studies for Walther lab were concerned with the objective motor activity, the low level of motor activity in SZ patients observed SZ cognitive performance is associated with similar clinical and neural correlates that reported for objective motor activity. SZ patients show increased RT during cognitive performance. Furthermore, it has been suggested that processing speed deficiency is a core factor for the other affected SZ cognitive performance. Previous studies emphasized that SZ patients are slower than HC subjects on a range of cognitive tasks. In Schatz (1998) meta-analytical study 1998, the author examined reaction time data across 196 reaction time conditions in 40 studies. The proportional relationship between the response times of groups with SZ was compared to HC. Using a regression approach, the general processing speed, was compared with possible domain-specific or task specific deficits. The results suggested that the data conforms a general linear slowing model. It accounted for 87% of the variance in reaction time performance. Some additional variance was accounted for by different degrees of linear slowing for three types of task performance: tasks involving selective attention/inhibition showed the most slowing, followed by lexical tasks, and finally, non-lexical tasks (Schatz, 1998). Looking more specifically inside the scanner, it was proposed that SZ patients demonstrate increased hypofrontality

when they exhibit greater performance deficits relative to HC, while they exhibit intact or increased activity at higher levels of performance (Callicott et al., 2000; Manoach, 2003). Previous findings revealed that the increased reaction time was strong predictor of hypofrontality as well as the decreased accuracy. Van Snellengberg at al. (2006) reviewed studies that utilized functional MRI or positron emission tomography, included both SZ patients and healthy control groups, conducted scanning under conditions other than a resting state, auditory verbal hallucination, or pharmacological challenge, and tested the between-group difference in activation of DLPFC or the reported data that permitted an estimation of this difference. Because of the substantial heterogeneity in the data, average effect sizes were estimated with a random-effects procedure. For each study, the standardized effect size (Cohen's d) was estimated for accuracy and, reaction time, as well as DLPFC activation. SZ patient samples were significantly impaired in both accuracy and RT. It was also indicated that Patients exhibited increased hypofrontality when they exhibited greater performance deficits than HC subjects did. Comparing to accuracy, reaction time was a strong predictor of group differences in DLPFC activation. Reaction time continued its predictive power regardless of the other variables in the model, particularly for the DLPFC analyses (Van Snellenberg, Torres, & Thornton, 2006).

Later on, increased reaction times in SZ associated with decreased DLPFC activity have been explained as proactive control deficiency (Barch & Sheffeild, 2014; Fassbender, Scangos, Lesh, & Carter, 2014). Unfortunately, that was not a consistent pattern of response SZ patients show during the task. As shown in previous section, the

decreased activity of DLPF as well as other cortical regions is not consistent findings. The same for the reaction time data, although there is strong evidence on the increased reaction times in SZ, other findings showed intact reaction times. It was also suggested that the intact RT during simple RT tasks was associated with increased brain activity in some regions. Minzenberge et al. (2012), found that SZ patients were not different from HC subjects in reaction time to a simple reaction time task. However, subjects with SZ showed significantly higher activation in primary motor cortex and adjacent premotor and somatosensory cortices, and significantly lower activation in bilateral basal ganglia. These findings show evidence on excessive neural activity in motor cortex contralateral to the primary motor cortex in SZ, which may form the basis for altered motor laterality and motor overflow previously observed, and disorganized behavior (Minzenberg, Yoon, Soosman, & Carter, 2012). These findings could be explained by the compensatory mechanisms hypothesis I discussed in previous sections. SZ patients were able to activate motor areas in the brain to compensate for other deficient mechanisms. As illustrated in previous sections, previous studies that utilized higher cognitive tasks can show intact or increased brain activity in SZ patients associated with improved performance (Callicott et al., 2000; Manoach et al., 1999). These findings together shed light on compensatory mechanisms that SZ patients may adopt to achieve a certain level of task performance. According to these findings, SZ patients trade time for accuracy compensating for a cognitive deficiency.

The question now is: Do SZ patients using the same compensatory mechanisms during the same task? Do they show a stable pattern of performance during the same

task? Although SZ patients show a wide range of cognitive disturbances, there is growing evidence on fluctuating pattern of behavioral performance during cognitive tasks. Specifically, comparing to HC, SZ patients show increased reaction time intra-individual variability (RT-IIV) - across trials. In the next few pages I will discuss RT-IIV and the neural alterations associated with it in healthy and SZ patients.

Reaction Time Intra Individual Variability (RT-IIV) in Schizophrenia.

Previous investigations have focused on individual and group differences in measures of central tendency such as mean response time (RT) or accuracy. Recently, several behavioral investigations have shown that measures of RT-IIV can provide information about performance that is not detectable by the mean (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008). RT-IIV reflects a transient trial-to-trial change in behavioral performance. It is a common component of behavioral changes associated with neurodegenerative and other brain-related disorders such as traumatic brain injury as well as SZ (MacDonald, Nyberg, & Bäckman, 2006).

In neuropsychological task performance, intra-individual reaction time variability reflects short-term fluctuations in performance. It may be an important index of the efficiency with which executive control processes are implemented. For along time, it has been used as a measure of attention lapsing, and mind wandering (Fassbender, Lesh, Ursu, & Salo, 2014) as well as cognitive instability (Cole, Anticevic, Repovs, & Barch, 2011). High levels of RT variability have also been associated with an inability to effectively engage cognitive control in situations of increased cognitive demands (Bellgrove, Hester, & Garavan, 2004), and sustained attention impairments (Hervey et

al., 2006).

Increased RT-IIV in comparison to HC subjects has been noted in diseases associated with deficits in cognition, including SZ (Fassbender, Scangos, et al., 2014). As individuals with SZ show general slowness relative to HC subjects across cognitive tasks (Morrens, Hulstijn, & Sabbe, 2007 & Vinogradov et al., 1998), they also show higher reaction time within-subject and between-subject variability. Furthermore, it was noted that mean RTs and RT-IIV are independent in SZ. Using a lexical decision choice reaction time (CRT) task, Vinogradov at al. (1998) explored the relation of mean CRT and its IIV to performance on executive-motor tasks in 26 medication-free SZ patients and 17 normal comparison subjects. SZ patients had both significantly slower and more variable CRTs that were unrelated to general intellectual abilities. Among SZ patients, both CRT and CRT-SD were significantly related to the failure maintaining cognitive task. Slower CRT was related to Global Assessment of Functioning Conceptual Disorganization, Mannerisms and Positive Symptoms. After controlling for mean, increased CRT-SD was associated with Global Assessment of Functioning, Conceptual Disorganization and Positive Symptoms. It also showed a significant positive association with Tension/Hostility Symptoms. However, mean CRT showed unique covariation with the failure to maintain cognitive set and with stereotypic mannerisms (Vinogradov et al., 1998). In addition, it has been found that the increased intra-individual reaction time variability is highly sensitive to cognitive deficits in SZ. In Rentrop et al. (2010) study, 28 high-functioning SZ patients and 28 HC subjects performed a Go/Nogo task and a CPT. IIV differentiated consistently and with large effect size between groups. Modeling

with an ex-Gaussian distribution revealed that patients have a higher proportion of slow responses reflected by an increased tau parameter (exponential component). The author concluded that IIV was highly sensitive to cognitive deficits not directly visible in a high-functioning SZ group. They suggested that response pattern with more exceedingly slow reactions could reflect a core deficit in the stability of information processing (Rentrop et al., 2010).

Similarly, Kaiser et al. (2008) compared IIV measures obtained in a Go/No go task from SZ patients, major depression, and borderline personality disorder. IIV was increased for SZ patients. All groups showed a strong association between IIV and accuracy of task performance. The results including measures of intra-individual reaction time variability, mean reaction time and accuracy showed differential patterns for SZ patients compared to those with borderline personality disorder or depression. SZ patients exhibited more RT with increased vraibility relative to the other groups (Kaiser et al., 2008).

Increased RT-IIV in SZ doesn't sound to be related to specific motor system. Karantinos et al. (2013), applied RT tasks requiring basic sensorimotor processing and engaging two different motor systems: a Finger Lift Reaction Time task and the Voluntary Saccade Reaction Time task. The ex-Gaussian model was applied to the reaction time distributions estimating mu, sigma and tau. In both tasks, a significantly larger RT-IIV effectively dissociated patients from HC. The RT-IIV for both tasks was highly correlated for patients but not for HC. Both sigma and tau were significantly higher in the SZ patients with tau being the best predictor of SZ. Sigma and tau were

highly correlated between the two tasks in SZ group. The results reflect a deficit in the context processing that may indicate dysfunction in distributed neural networks modulating adaptive regulation of performance (Karantinos et al., 2014)

Interestingly, the increased RT_IIV in SZ is uncontrollable. In a recent study for Kappermann et al. (2015), the authors used behavioral measures and event-related potentials to test for specific impairment in SZ during the performance. 22 SZ patients and 22 healthy participants completed a choice response task that emphasized the accuracy (unspeeded condition) or emphasized accuracy, as well as speed (speeded condition). By contrast to HC, SZ patients were unable to reduce their RT or its variability or to modulate the lateralized readiness potential under speed pressure condition, despite showing decreased accuracy. Response-related deficits in SZ emerged only in the speeded condition; behavioral and ERP measures did not differ between groups in the unspeeded condition.

Furthermore, RT-IIV is still a hallmark in SZ patients even when they have equal or decreased RT. Smyrnis et al. (2007) found that SZ patients showed increased RT-IIV and intra-group variability of RTs. In this study, median RT and its variability were measured for visually guided saccades performed by 53 patients and 1089 HC. Then average cumulative RT distributions were derived for each group. There was a small increase in the median RT for patients while their RT were more variable from trial to trial leading to a difference in the average RT distribution of the patient group. The authors concluded that this difference in the distribution of RT for patients could be attributed to a basic difference the context processing leading to the decision to move the

eyes to the visually presented target (Smyrnis et al., 2009). Also, In Carroll et al (2009) study, 32 subjects with SZ and 31 non-psychiatric control participants completed a repetitive finger-tapping task, which required participants to first tap in time with computer-generated tones separated by a fixed inter-tone interval (tone-paced tapping), after which the tones were discontinued and participants were required to continue tapping at the established pace (self-paced tapping). Participants with SZ displayed significantly faster-tapping rates for both tones, and self-paced portions of the task compared to the non-psychiatric group. At the same time, SZ patients displayed greater tapping variability during both tasks (Carroll, O'Donnell, Shekhar, & Hetrick, 2009)

Large literature of RT in SZ indicated its increased variability. Despite these findings, very few studies have been concerned with investigating cognitive and neural aspects mediating these variations. It is intuitive that behavioral changes within an individual can reflect alterations in the cognitive and the neural processes. Monitoring RT-IIV can, therefore, provide an understanding of the underlying mechanisms (MacDonald et al., 2006; Yarkoni, Barch, Gray, Conturo, & Braver, 2009). In the next section, I will discuss studies that have linked RT-IIV to brain activity in both healthy and SZ groups.

Findings of Neural Alterations Associated With Reaction Times Intra-Individual Variability (RT- IIV).

Previous studies have suggested that patients with an injured frontal lobes show increase RT-IIV. An event-related fMRI design and a Go/No-go response inhibition task in a group of HC subjects revealed that individual differences in Go response time

variability were a strong predictor of inhibitory success (Bellgrove et al., 2004). In comparison, the differences in mean Go response time could not account for the same effect. Task-related brain activation was positively correlated with RT-IIV in an inhibitory network including bilateral middle frontal areas and right inferior parietal and thalamic regions. The authors concluded that subjects with higher RT-IIV activated inhibitory regions to a greater extent.

Similarly, in Hahn et al. (2007), participants responded to targets presented randomly in one of four peripheral locations. By utilizing a function of reaction time across trials as a linear regressor, brain regions activation was investigated with RT on a trial-by-trial basis. Through a whole-brain analysis, the results revealed hyperactivation of the anterior cingulate, posterior cingulate and left angular/superior temporal gyrus in trials with faster RT, but only when the target location was unpredictable. Interestingly, this association was not seen in trials with a predictable target location using a central cue. These findings were consistent with previous findings on the cingulate and perhaps the angular gyrus in attention control to unpredictable events.

In Yarkoni et al. (2009), the relation between trial-by-trial differences in RT and brain activation was modeled in five different fMRI datasets with different stimulus modalities. The authors pointed out three main results. First, activation was delayed on trials with long RT relative to short RT. Second, in lateral and medial frontal regions, activation showed a ‘‘time-on-task" effect, increasing linearly as a function of RT. (Yarkoni et al., 2009)

Another study found RT-IIV to be negatively associated with ACC activation.

Johnson et al. (2015) applied whole-brain multiple regression for each subject using absolute RT deviation for all correct go-trials; all no-go trials and trials in which an error was made were included as regressors. The authors found a negative relationship between BOLD activation in a cluster within the left anterior cingulate (ACC) and RT-IIV, such that greater absolute deviation of RT from the mean was associated with reduced BOLD activation in the left ACC (Johnson et al., 2015).

Interestingly, regions reported above are also consistently reported as impaired in SZ patients (Minzenberg et al., 2009). At the same time, to our knowledge, few studies have correlated activation of these regions to reaction times. For the first time in SZ research, Fassbender et al., 2014 investigated the correlation between BOLD response and RT-IIV. The authors examined proactive and reactive control in SZ, as measured by reaction time (RT) variability, and long RTs during Stroop paradigm. The authors also examined the neural underpinnings of lapses in proactive control and the subsequent engagement of reactive control in SZ patients. IIV was estimated for each subject in each condition. In addition to examining the variability of the Gaussian component (σ) and the exponential component (τ), a combination of the two was used to estimate IIV: [$IIV = \sigma + \tau$]. Trial-by-trail approaches were utilized to investigate neural associations. The authors found that SZ patients exhibited greater RT-IIV and increased RTs relative to HC. All of the subjects activated areas of the cognitive control network during long RTs, consistent with an engagement of reactive control following a failure to manipulate a proactive control on these trials. DLPFC, IPL and ACC showed group by RT significant interaction effect. During the slow trials, SZ group displayed significantly diminished

activity in these regions relative to HC subjects (Fassbender, Scangos, et al., 2014). Fassbinder findings highlighted the same regions previously reported to be associated with increased RT-IIV as well as increased activation in SZ patients relative to HC. We suggest that these to be associated with different cognitive mechanisms subjects adopt during the task to compensate for failures in the original proactive mechanism.

In the following section I will introduce hypothetical cognitive/neural mechanisms in SZ suggesting the trial-to-trail approach for investigation them. I will shed the light on the importance of this approach.

Neural/Performance Correlates in Schizophrenia as Compensatory Mechanisms.

In the current project, I suggest that linking behavioral performance fluctuations reflected by RT to the neural alterations would help solving the inconsistent neuroimaging findings in SZ. It would also help understanding the underlying mechanisms and whether they are early reactive, late reactive or proactive. Identifying different patterns of the performance reflected by RT during accurate/inaccurate performance associated with variable patterns of neural activity would help to understand the cognitive mechanisms associated with each pattern.

Hypothetical Compensatory Mechanisms In Schizophrenia

Previous findings in SZ indicated that subjects with SZ show increased IIV (e.g. Kaiser et al., 2008; Rentrop et al., 2010), as well inconsistent neuroimaging findings and increased variability of the homodynamic response have been reported in SZ literature. As the increased reaction time could indicate a deficient proactive control mechanism in SZ, the increased RT-IIV parallel to the increased intra-individual hemodynamic

response variability raises important questions to be investigated: What are the neural alterations associated with this variability? Do SZ patients adopt different mechanisms with different response times during the same task? Do patients shift between proactive and reactive mechanisms during the task? What are the neural alterations for each mechanism?

Hypothetically, according to the integrative approach I adopt in the current paper, the integrative expected patterns of performance should be one of the following: 1- Intact RT and Intact accuracy " intact errors rate" (0RT/0ER). For this pattern, I expect the proactive control to be unimpaired. The subject was able to maintain the task successfully and to activate the relevant control regions (such as DLPFC) as well as HC; 2. Intact RT and affected accuracy " increased errors rate" (0RT/+ER), the proactive control is impaired, and the subjects rely on early reactive control. For this pattern of performance, subjects fail to neither activate cognitive control regions nor other compensatory cerebral mechanisms; 3. Affected RT and intact accuracy (+RT, 0ER): increased RT associated with decreased accuracy would reflect an efficient reactive mechanism. In this pattern of performance, subjects are expected to fail activating DLPFC while different compensatory related regions are activated (e.g. IPL, ACC); 4. Affected RT and affected accuracy (+RT/+ER): Increased RT and decreased accuracy reflect inefficient reactive mechanism. The subjects fail to activate DLPFC while different compensatory unrelated regions are activated (e.g. Cerebellum, Basal Ganglia; Fig 1-5).

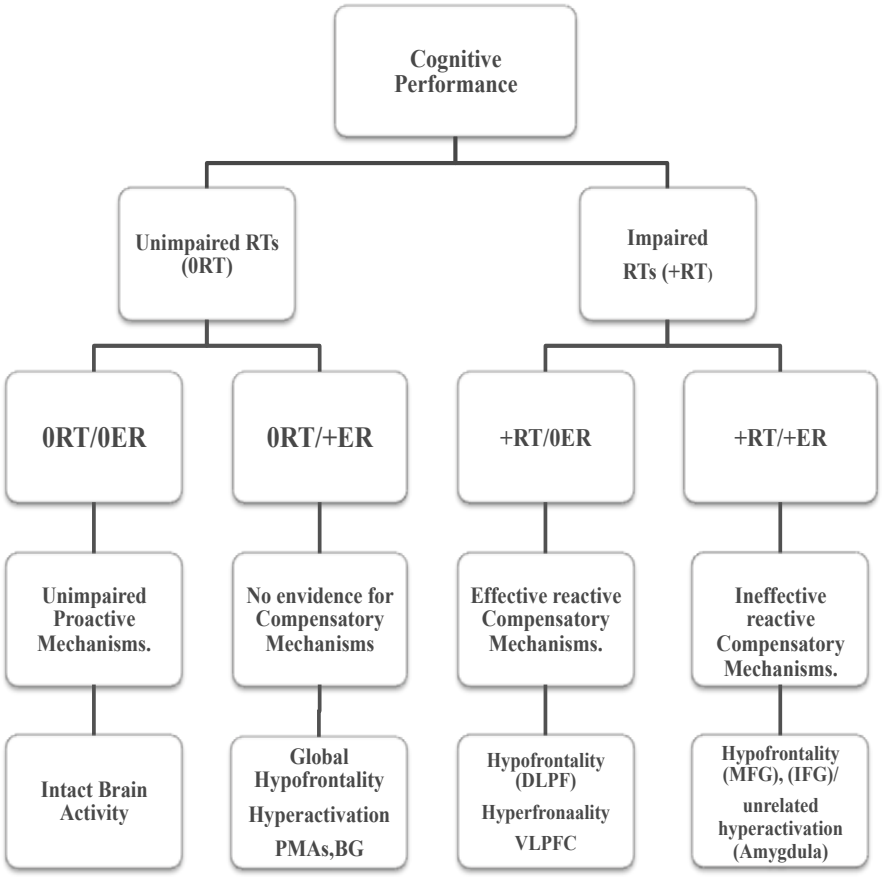


Fig. 1-5 *Hypothetical assumptions about the cognitive/neural mechanisms reflected accuracy and RTs in SZ.*

For investigating these hypothetical mechanisms, I suggest linking variable performance -as reflected by RT- to the brain activity. The common approach of averaging RT for each subject will not be as accurate as trial- to trial analysis in the current assumptions.

Motivation For the Current Study

In this chapter we have shed the light into cognitive impairments in SZ that suggested to be driven by proactive control deficiency (Barch & Ceaser, 2012). We also

highlighted the functional and neuroimaging inconsistency in SZ research. Also, we illustrated previous evidence on increased RT variability in SZ focusing on RT/ neuroimaging correlation in HC subjects and SZ patients. Then we set our hypothetical model to test the correlation between RT variability in and brain correlates in in HC subjects and SZ patients.

These considerations provide the background for the current set of studies in which we will use RT-IIV and the neural alterations associated with them to determine whether these provide insight into hypothetical compensatory mechanisms in SZ patients. In Chapter 2 I will more systematically examine the neuroimaging literature in SZ. I will use this as a principled means to establish those regions where patients show consistent deficits, and therefore provide the best brain candidates for a priori analyses linking IIV metrics to impaired or compensatory mechanisms. Chapters 3-5 describe the methods, behavioral results and neuroimaging results from an archival study of SZ patients and their first-degree relatives who performed a cognitive control task.

Specific Aims & Hypotheses

Aim and Hypothesis 1

Aim1: Utilizing a meta-analytic approach, the first aim of the current study is to investigate differences in neural alterations between impaired vs. unimpaired reaction times during cognitive tasks in SZ compared to HC. Previous meta-analytical studies were concerned with investigating (BOLD) response across different domains of cognitive performance in SZ patients (Glahn et al., 2008; Minzenberg et al., 2009a). Although those studies helped decrease the heterogeneity of the neuroimaging data, they

didn't fully address the heterogeneity of performance. While the included studies in these analyses reported the data of the correct trials only, they include both impaired and unimpaired reaction times. Also, the finding of these studies showed hypo and hyper activation in SZ groups. While the decreased activation is related to the cognitive deficits the patients have, hyperactivation has been explained as a compensatory mechanisms (Minzenberg et al., 2009a). As mentioned before, compensatory mechanisms are more likely to be reactive mechanisms that drive more time and wider and more brain activity to complete a task (Barch & Sheffeild, 2014; Braver, 2012). For these two reason, I expect to see increased neural activity in SZ (relative to HC) in the studies that reported impaired RT--but not in the other studies with unimpaired RT – reflecting compensatory mechanisms.

Hypothesis1: Based on the previous fMRI meta-analyses findings (Minzenberg et al., 2002; Glahn et al., 2005), I hypothesize that studies showed impaired RTs in SZ groups would show increased activity in different VLPFC regions as compensatory activation.

Aim and Hypothesis 2

Aim2: The present study is concerned with testing reaction time variability - not as a uninformative 'noise', but as an evidence on the stability of cognitive processing (Rentrop et al., 2009). Although this approach is common in ADHD research, few SZ studies have tested RTs' variability as the main concern. The second aim for the current study is testing RT-IIV in individuals with SZ and SZ.R and whether they are different from HC. In addition, the current paper is also concerned with the relationship between

the increased RT-IIV in SZ and their clinical and cognitive disturbances. While there is considerable evidence on the increased RT intra-individual variability (RT-IIV) in SZ, few studies have been concerned with the correlates between this fluctuating performance SZ and the other pathological symptoms including cognitive and clinical symptoms.

Hypothesis 2a: SZ patients and SZ.R will exhibit more RT-IIV compared to HC groups.

Hypothesis 2b. RT-IIV will be correlated negatively to the overall accuracy percentage.

Hypothesis 2c. RT-IIV will be correlated positively to the clinical symptoms (negative, disorganized and positive symptoms) in SZ patients.

Aim and Hypothesis 3

Aim3: Although previous studies illustrated that SZ patients exhibit increased reaction times variability, few studies were concerned with investigating the behavioral and neural characteristics of these mechanisms. Linking the variables of "behavioral performance" and "brain activity" together may be helpful to understand the cognitive disturbances and the compensatory mechanisms that account for abnormal RT-IIV in the SZ literature.

Hypothesis3: I hypothesize that different levels of RTs will reflect different pattern of activations within groups. Also, I hypothesizes, that SZ patients will slow more activation during the slow performance than the fast relative to HC.

In the next chapter, I conduct Activation likelihood Estimation meta-analysis study. My first concern in that study is to determining on the most consistent

neuroimaging findings in SZ literature. Then I conduct ALE analyses separately within studies with impaired vs. groups with unimpaired RTs to test brain correlates to RT intra group variability.

Chapter 2 Brain correlates with cognitive performance in schizophrenia: Activation likelihood Estimation

Foreword: This chapter was written in collaboration with Angus W. MacDonald, who edited and revised versions of the manuscript.

Abstract

In the current study we were concerned with understanding the brain activity alterations in SZ patients during executive tasks. We, therefore, utilized a quantitative meta-analysis approach including 90 published studies. Activation likelihood estimation within and between groups was applied using Ginger_ALE software. Furthermore, to solve for performance heterogeneity, we divided the included studies to studies into impaired and unimpaired RTs. We, then, conducted activation likelihood estimation (ALE) analyses to each set of foci separately. Our findings supported our hypothesis that SZ patients had decreased activation in DLPFC, they aslo showed increased VLPFC activation relative to HC. Further more, the increased patterns of increased activity in SZ patients was replicated only across studies that reported impaired RTs in SZ patients relative to HC. Only Primary motor cortex and cingulate gyrus were replicated across studies with unimpaired RT.

Introduction

Previous meta-analytical studies were concerned with investigating (BOLD) response across different domains of cognitive performance in SZ patients (Glahn et al., 2008; Minzenberg et al., 2009a). Those studies reported decreased and increased patterns

of cortical activity in SZ patients compared to HC. They mainly showed decreased activation in DLPFC regions. At the same time, they showed increased activity in right IPL and Left ACC regions. Although those meta analyses across all task highlighted the most consistent neuroimaging findings from previous studies in SZ literature, they do not address the source of heterogeneity across those studies. In Minzenberge et al., (2009) study, the authors applied ALE analyses separately for different cognitive domains to solve for tasks heterogeneity. However, even within the same domains, the analyzed were more likely to be heterogeneous. While the included studies in those analyses reported the data of the correct trials only, they include both impaired and unimpaired reaction times. In the current work, we had two aims: First, we aimed to replicate previous neuroimaging finding in SZ by applying activation likelihood estimation to the available neuroimaging findings; second. we hypothesized that heterogeneous performance (impaired/impaired RTs) would reflect heterogeneous patterns of brain activity. We suggested that group with impaired RTs relied more on reactive compensatory mechanism showing increased VLPFC activity.

Methods.

We utilized a Meta analysis to investigate our hypothesis using Activation likelihood Estimation (ALE) across number of the previous neuroimaging studies in SZ.

Study Selection.

A systematic search strategy was adopted to identify relevant studies. We carried out a PubMed search using the following keywords: SZ, FMRI, PET, executive functions or cognitive functions. Studies were considered for inclusion if they are published before

2014 in article format, if they utilized FMRI or PET data analysis to investigate functional differences in whole brain structures, and if they reported three dimensional coordinates and both reaction times and accuracy effect sizes. 1516 studies were found with searching words: " (Schizophreni*) AND (fmri OR bold response) AND (executi* OR cogniti*) – Filtered to journal article, human, English, abstract). Manual abstract inspection excluded irrelevant studies, and kept the studies that were concerned with BOLD responses during cognitive tasks in SZ.

Parallel to the PubMed search, a sleuth functional database search was also conducted with the following search criteria (Subject> Diagnosis> schizophrenia, experiments > behavioral domains > cognitive > all subtypes). The search retrieved 98 studies with 409 experiments. After manually reviewing all experiments and excluding the unrelated papers and experiments, we included 84 papers with 337 experiments that tested 2343 subjects and retrieved 3538 foci.

Studies included in the overall analysis: Summing up Sleuth search findings to PubMed search findings, 90 studies, 122 experiments, 2565 subjects and 4849 foci studies were included in the current analysis. For each experiment, text files of the activated foci were created (Manually for the PubMed articles and automatically for the sleuth articles). For PubMed studies with MNI foci, foci were transformed to Talairach space mapping using the Lancaster transforms, icbm2tal in GingerALE (Landcaster et al., 2007).

Activation Likelihood Estimation Analyses.

The current meta analyses were conducted using Activation Likelihood

Estimation (ALE). ALE is a meta-analytic tool that models 3-dimensional coordinates (from reported activations in a standard space) as the center of a 3-dimensional Gaussian distribution (Laird et al., 2011; Turkeltaub, Eden, Jones, & Zeffiro, 2002). In the current paper multiple ALE analysis were conducted using Brain Map GingerALE version 2.3.6. As per current recommendations for the software, all maps were thresholded to $p < .001$ with an extent cluster threshold greater than 400mm. We used Turkeltaub non-additive method to minimize within experiment and within group effects (Turkeltaub et al., 2012).

In the current study, we tested for within- and between-group activity across all the cognitive experiments and between group across impaired/unimpaired RTs as follows:

1. Across all the cognitive experiments we ran within-group and between-groups ALE analyses. Foci were pooled in 4 separate text files – two files for within-group analyses (HC& SZ) and two files for group differences (HC > SZ & SZ >HC);

2. Studies were divided into two categories of response - impaired vs. unimpaired RTs- (Fig 2-1). We used effect size 0.3 as a cut point for unimpaired and impaired RT. Cohen'd effect sizes calculated as following: (SZ. RTmean - HC. RTmean / pooled SD) for each experiment. We then tested between-group brain activation (HC>SZ /SZ>HC) for each RT category (Impaired RT / Unimpaired).

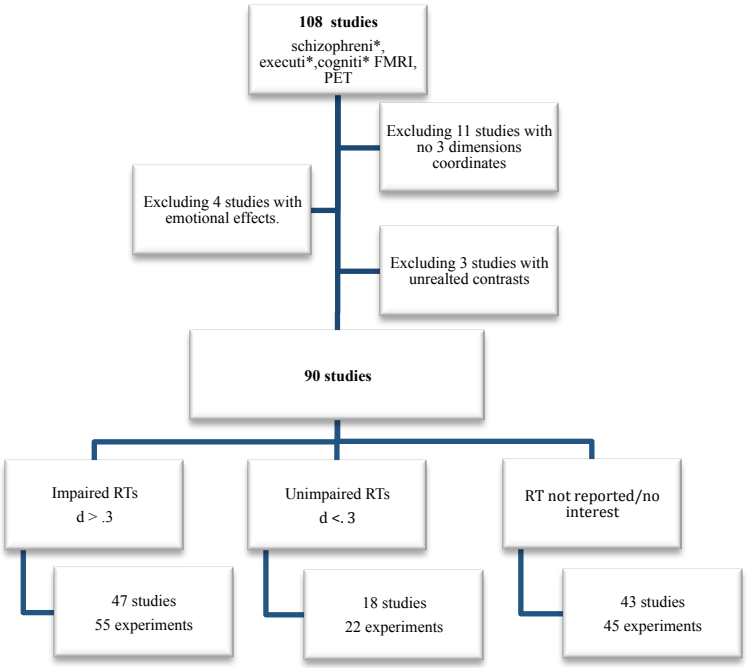


Fig. 2-1 *Total Studies included in ALE analyses: all and within RT categories (Appendix1 for details).*

ALE - across all studies.

Within groups analyses. Analysis was conducted across (2125) foci that were reported to be active in SZ patients in 90 study, 122 experiments with 1251 subjects. Similarly, separate ALE analysis was conducted for HC groups including (2008 foci) from 130 experiments that tested 1202 subjects (Appendix 1).

Between groups analyses. (SZ Patients vs. HC), ALE analysis was conducted for the foci of the contrast HC > SZ. The analysis included 423 foci from 78 experiments that test 1168 subject. While the contrast SZ > HC had 330 from 70 studies that tested 1005 subjects.

ALE- across RT categories (impaired RT/ unimpaired RT).

ALE analyses were conducted for two categories of performance impaired RTs vs. unimpaired RT. For each category ALE was conducted only between groups as follow: 1. Across Impaired RTs experiments, the analysis for HC>SZ contrast included 644 foci from 57 experiments, while the analysis of SZ > HC included 489 foci from 32 experiments; 2. Across unimpaired RTs experiments, HC>SZ analysis included 322 foci from 24 experiments for unimpaired RTs, and the analysis of SZ>HC contrast included 230 foci from 23 experiments

Results

Across all studies

Within group analyses. In the current study we quantitatively analyzed 90 fMRI previous published studies in SZ cognitive performance. Both SZ and HC groups showed similar patterns of brain activation that included wide range of cortical activation included bilateral DLPFC, ACC, parietal and occipital cortex activation (table 2-2, Fig. 2-2).

Table 2-1 Brain regions showed more activation in (HC > 0) experiments and (SZ >0) experiments (p=. 001)

Brain Regions	**Volume**	**Max. value**	**Weighted Center**			**BA**
			X	Y	Z	
HC						
L. Middle frontal gyrus, L. Inferior frontal gyrus, L. precentral gyrus, L.Thalamus, R. Thalamus.	29040	.078	-31.2	6.2	20.7	6,9,46
R. Middle frontal gyrus, R. Precentral gyrus.	13800	.07	40.3	11.5	35.2	6,9

L. Medial frontal gyrus	8512	.09	-0.3	11.6	44.2	32
R. Insula	6192	.07	33.4	18.1	3.4	13
L. Inferior/superior parietal lobule	5984	.07	-33.6	-57.9	41.2	40,7
R. Inferior parietal lobule, R. Precuneus	5520	.058	33.8	-57.3	39	40,19
R. Middle temporal gyrus	608	.04	33.6	-74.5	19.1	19, 31
R. Middle frontal gyrus	512	.04	35.4	46.8	14.3	10
SZ						
R. Inferior frontal gyrus, R. Insula, R. Middle frontal gyrus, R. precentral gyrus	19064	.07	37.9	13.9	24.5	9, 45, 13 46, 6
L. Inferior frontal gyrus, L. Insula, L. Middle frontal gyrus, L. precentral gyrus	18624	.07	-39.4	10.6	25.1	9, 45, 13 46, 6
R. Cingulate Gyrus	8368	.08	0.2	11.6	44.5	32
R. Inferior parietal lobule, R. Superior parietal lobule, R. Angular gyrus	6968	.07	35.5	-53.2	42.2	40, 39, 7
L. Inferior parietal lobule	6448	.06	-34.5	-58.1	40.5	40,7, 19
R. Thalamus, L. Thalamus (ventral anterior nucleus)	4288	.04	-0.8	-9.4	8.7	
L. Inferior parietal lobule, L. postcentral gyrus-parietal lobe	1896	.04	-42.4	-29.5	48.1	40, 3
L. Superior temporal gyrus, L. postcentral gyrus-parietal lobe	648	.038	-53.6	-24.7	11.9	40,41
R. Superior temporal gyrus	640	.037	56.3	-36.2	7.7	22
L. lentiform nucleus-putamen	616	.04	-14.6	7.8	4.1	
L. Superior temporal gyrus	560	.04	-51.4	-37.5	12.4	22
L. Precentral gyrus-frontal lobe	504	.035	-53.5	-8.8	12.6	43
L. Superior temporal gyrus	488	.043	-38.9	-57.8	-14.7	38

Note: L left hemisphere, R right hemisphere, SZ schizophrenia patients, HC healthy controls.

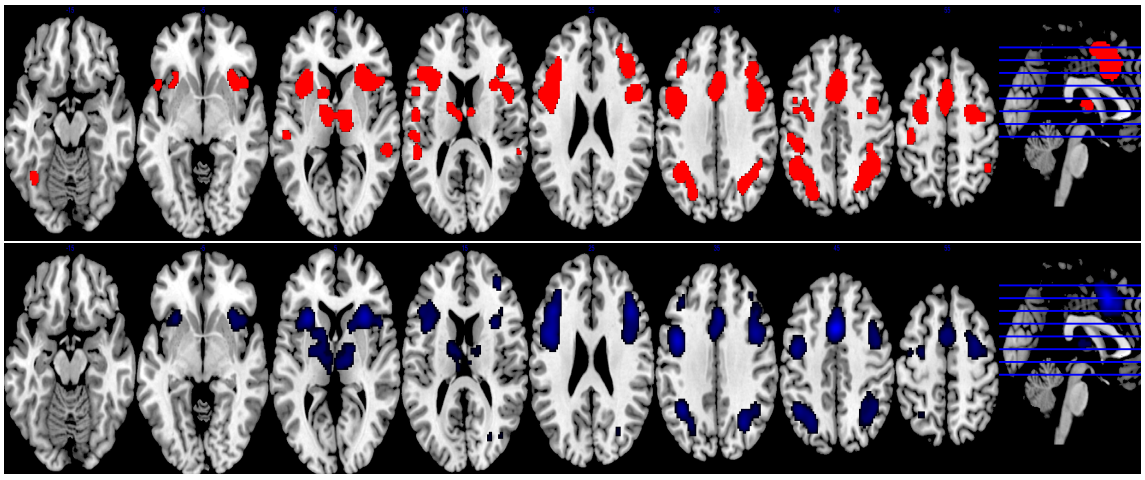


Fig. 2-2*. ALE within groups – uncorrected voxel wise analysis p=.001*. Activation within SZ patients (Red), Activation within HC (Blue).

Between Groups Analysis. Using the currently recommended threshold level (p<.001), HC groups showed increased activation in inferior frontal gyrus area (9, 46, 47); Superior frontal gyrus area (6), Middle frontal gyrus 9, inferior parietal lobule area (7), insula area (13) and the right cingulate gyrus area (32) compared to SZ patients (table 2-3). On the other hand, SZ patients showed increased activation in smaller clusters included left cingulate gyrus area (32, 24), middle occipital lobe (19), left precentral gyrus (4), and right postcentral gyrus (3), (table 2-3 & Fig 2-2).

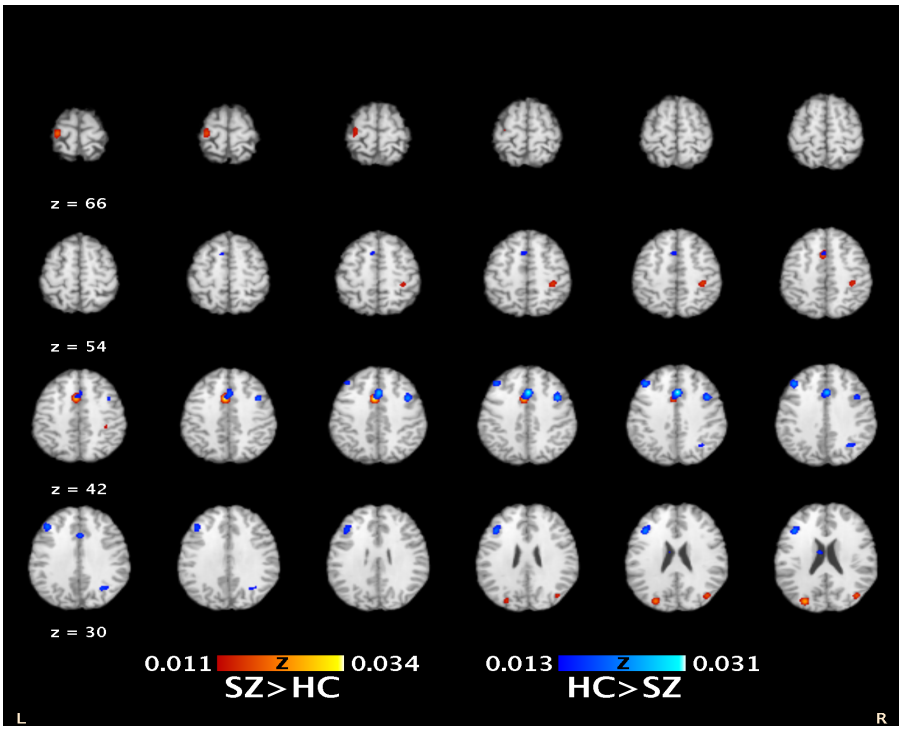
Table 2-2 Brain regions showed more activation in (HC > SZ) experiments and (SZ > HC) experiments (p=.001)

Brain Regions	**Volume**	**Max. Value**	**Weighted Center**			**BA**
			X	Y	Z	
HC>SZ						
R. Claustrum /Inferior frontal gyrus	2848	.028	31.1	23.2	6.1	NA/13
L. Middle frontal gyrus/ Insula	2712	.021	-38.3	27.6	24.1	9/46/13

R. Thalamus	2136	.022	-3.2	-9.3	11.4	NA
R. Cingulate gyrus, L. Medial frontal gyrus	2096	.02	0.7	15	37.3	32, 6
R. Precentral gyrus	944	.03	39.9	10.1	36.3	9
L. Claustrum	576	.022	-28.2	20.4	-0.7	Na
R. Middle temporal gyrus	400	.021	32.6	-62.2	30.9	39
SZ > HC						
L. Cingulate gyrus	1536	0.03	-3	8.4	39.2	32
L. Middle occipital gyrus	936	0.025	-26.4	-82.2	19.3	19
L. Precentral gyrus	808	0.02	-27.3	-22.4	65.7	4
R. Postcentral gyrus	552	0.016	34.3	-34.1	46.4	3
L. Anterior cingulate gyrus	432	0.021	-3.2	37.3	-0.6	24
R. Middle temporal gyrus	400	0.02	40.2	-73.9	21	9

Note: L left hemisphere, R right hemisphere, SZ schizophrenia patients, HC healthy controls.

Reported Coordinates are in Talairach space.



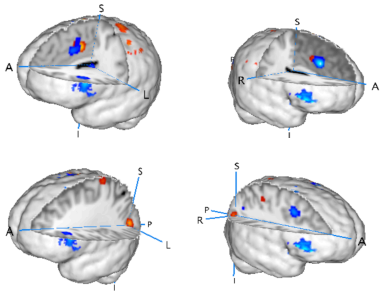


Fig. 2-2 *brain activation for groups contrasts*. HC > SZ and SZ > HC.

Contrasting – Subtracting analysis. Further more, to compare SZ groups set of foci vs. HC groups set of foci and examine them for statistically significant differences in convergence; we conducted ALE contrast (subtract) analysis. By contrasting the activated foci in SZ groups to the activated foci in HC (ALE contrast analysis), consisting with our single studies ALE analysis, groups showed overlapping activation in a wide cortical set of voxels that included left MFC, IFG, thalamus, postcentral gyrus, right inferior parietal lobe, right middle temporal gyrus, right middle occipital gyrus and right superior temporal gyrus (table 2-4). On the other hand, unlike SZ patients, HC subjects activated right and left middle frontal cortex, while SZ patients activated left inferior parietal lobule and left precentral gyrus (table 2-5).

Table 2-3. Brain regions showed activation in both groups (HC and SZ).

Brain Regions	**Volume**		**Weighted Center**			**BA**
			X	**Y**	**Z**	
L. Inferior frontal gyrus, L. Middle frontal gyrus, R. precentral gyrus, L. Precentral gyrus, R. Postcentral gyrus , L. Postcentral gyrus L thalamus, R. Thalamus. R. Insula, R. caudate.	85392	.07	-1.7	9.3	21.2	6,9,13 , 39,41, 43,47

R. Inferior parietal lobule, R. Precuneus, R. Middle temporal gyrus.	13488	.05	32.8	-58.4	38.3	7, 19 , 31, 40
R. Cingulate gyrus.	12328	.08	-0.1	11.2	44.4	32
L. Superior and inferior parietal gyrus	10368	.06	-33.6	-58.7	40.8	7, 40
L. Superior temporal gyrus and postcentral gyrus	2000	.03	-51.8	-33.3	11.3	22,41
L. Middle temporal and middle occipital gyrus	1552	.03	-29	-78.4	19.9	17, 19
L. Posterior lobe	1344	.028	-37.4	-60.2	-14.8	18
R. Middle temporal gyrus	1072	.026	53.9	-38.2	7.2	22
L. Middle occiptal gyrus	744	.03	-30	-83.5	1.1	18
L. Lingual gyrus	560	.032	23.2	-86.4	1.3	17
R. Middle occiptal	504	.024	41.4	-65.7	6.1	37
L. postcentral gyrus	472	.022	-40.7	-27.8	46.7	3, 40
L. Middle frontal gyrus	432	.022	-33.8	50.3	11.8	10

Note: L left hemisphere, R right hemisphere, SZ schizophrenia patients, HC healthy controls.

Coordinates are reported in Talairach space.

Table 2-4 Brain regions showed more activation in SZ vs. HC (by contrasting thresholded images of activation in each group – ALE contrast analysis)

Brain Regions	**Volume**	**Max value**	**X**	**Y**	**Z**	**BA**
HC>SZ						
R. Middle frontal gyrus.	1560	2.9	45.4	20.7	27.1	6
L. Middle frontal gyrus.	1256	2.3	-42	-1.6	39.7	6
L. Thalamus-Ventral lateral nucleus, L. Lentiform nucleus	800	2.4	-22.8	-9.1	7.1	

R. Superior frontal gyrus, R. Middle frontal gyrus.	776	2.3	40.8	9	47.4	8, 6
R. Middle frontal gyrus, Cingulate gyrus	568	2.01	28	4	58	6, 32
SZ>HC						
L. Inferior parietal gyrus	1016	2.5	-37.1	-33.9	47.9	40
L. Precentral gyrus	536	2.3	-52.4	-6	13.7	4

Note: L left hemisphere, R right hemisphere, SZ schizophrenia patients, HC healthy controls. Coordinates are reported in Talairach space.

Impaired/Unimpaired RTs.

Unimpaired RTs. Across unimpaired RT studies (RT effect sizes < 0.3, 22 studies). Compared to SZ groups, HC showed increased activation in left MFG, left thalamus, right cingulate cortex, right claustrum, right precentral gyrus, right inferior parietal lobe. SZ patients showed increased activity only two regions: the left cingulate gyrus (32) and left precentral gyrus (6), (table 2-6).

Table 2-5 Unimpaired RT studies-Brain regions showed more activation in HC vs. SZ experiments (p=.001).

Brain Regions	**Volume**	**Max. value**	**Weighted Center**			**BA**
			X	**Y**	**Z**	
HC>SZ						
L. Middle Frontal Gyrus.	3416	0.02	-36.2	25	16.8	46
R. Claustrum	2512	0.02	33.5	25.1	7.3	NA
R. Precentral gyrus	792	0.02	40.6	10.9	35.5	9
R. Cingulate gyrus	784	0.02	2.2	17.8	34.9	32

L. Thalamus	656	0.017	-6.3	-10	14.8	
R. Inferior Parietal Lobule	504	0.016	35	-60.4	37.6	7
SZ > HC						
L. Cingulate Gyrus	1136	0.02	-3.4	7.6	39	32
L. Precentral Gyrus	483	0.02	-22	-26.5	61.7	6

Note: L left hemisphere, R right hemisphere, SZ schizophrenia patients, HC healthy controls.

Impaired RTs. Across impaired RT studies (RT effect sizes > 0.3, 46 studies), similarly to impaired RT studies, HC subjects exhibited increased PFC activation that included bilateral claustrum, left thalamus, left MFC, right cingulate gyrus and right precentral gyrus. Unlike unimpaired RT studies, SZ patients showed more clusters of increased activations. Those clusters included left cingulate gyrus (32), left anterior cingulate gyrus (24), left precentral gyrus (4), left middle occipital and temporal gyrus (19), right postcentral gyrus (table 2-7).

Table 2-6 Impaired RT studies, Brain regions showed more activation in HC vs. SZ experiments (p=.001).

Brain Regions	**Volume**	**Max. value**	**Weighted Center**			**BA**
			X	**Y**	**Z**	
HC>SZ						
R. Claustrum	2776	0.03	30.5	22.7	6.1	Na
L. Thalamus	2440	0.02	-3.4	-9.3	11.3	Na
L. Middle Frontal Gyrus	2320	0.02	-38.5	27.3	23.9	9
R. Cingulate Gyrus	1944	0.03	1	15.1	37.7	32
R. Precentral Gyrus	720	0.02	40.5	11.2	35.5	9

L. Claustrum	656	0.02	-28	20.4	-0.7	Na
SZ > HC						
L. Cingulate Gyrus	1688	0.03	-3	8.6	39.3	32
L. Middle Occipital Gyrus.	1032	0.025	-26.4	-82.1	19.3	19
L. Precentral Gyrus	888	0.02	-27	-21.5	65.7	4
R. Postcentral Gyrus	680	0.017	34.3	-34.4	46.4	3
L. Anterior Cingulate gyrus	560	0.02	-3.1	37.3	-0.4	24
R. Middle Temporal Gyrus	520	0.019	40.1	-73.8	20.9	19
L. Lingual Gyrus	472	0.019	-11.7	-68.7	-3.6	18

Note: L left hemisphere, R right hemisphere, SZ schizophrenia patients, HC healthy controls.

We then used ALE contrast analysis to contrast both set of foci (impaired RT SZ>HC vs. unimpaired RT SZ>HC) to each other. The two sets showed overlapping in one cluster that included left cingulate gyrus (32) with center X= -3.4, Y =7.6, Z= 39 and volume = 1132. On the other hand, the differences were not significant between the two sets of foci.

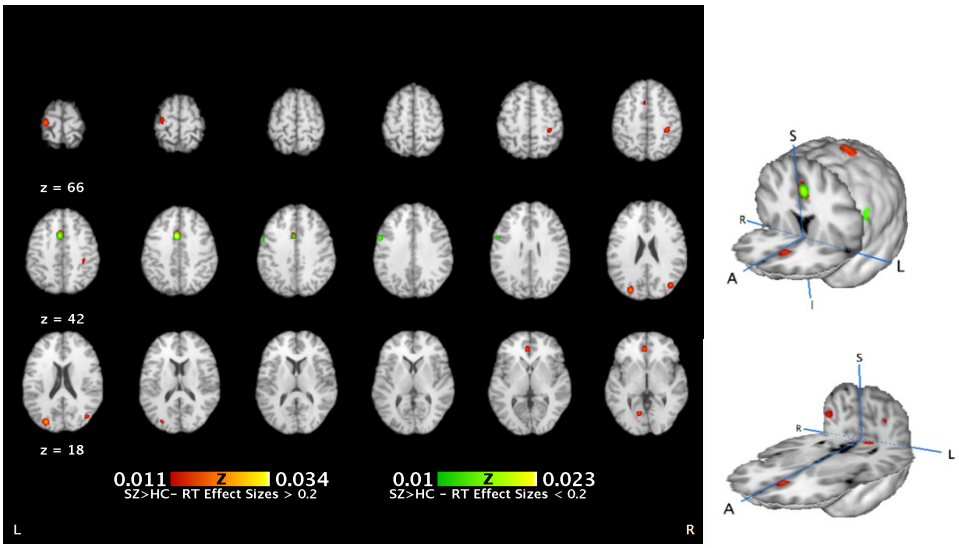


Fig. 2-3 SZ>HC; 1. *Across studies with impaired RTs (effect sizes > 0.3, Red),* ***2****. Unimpaired RT (effect sizes < 0.3 , Green).*

Discussion

The current meta analysis strongly supported previous results of decreased DLPFC activation in SZ patients relative to HC subjects (Barch, Csernansky, Conturo, & Snyder, 2002; Callicott et al., 1998; Carter et al., 1998; Jansma, Ramsey, Van der Wee, & Kahn, 2004; Mendrek et al., 2004; Perlstein, Carter, Noll, & Cohen, 2001). Moreover, replicating other previous studies, our findings highlighted regions of increased activation in SZ groups compared to HC. SZ groups showed increased activation in other regions that included left precentral gyrus, left anterior cingulate, left cingulate gyrus. Those findings of hyperactivations in SZ were suggested in previous literature to be compensatory mechanisms that patients adopt to deal with challenging cognitive tasks (Glahn et al., 2008; Manoach et al., 1999; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009b)

In the current study, our hypothetical model, we suggested that studies with impaired RTs vs. studies with intact RTs would show different patterns of group brain activation differences with increased VLPFC activity in studies with increased RT. We hypothesized that SZ patients will show increased activation relative to HC groups in the studies with impaired RTs but not in the studies with intact RTs. Our findings supported that hypothesis. Within 54 experiments with impaired RTs, SZ patients showed increased activation in cortical regions included left anterior cingulate gyrus (ACC), left precentral gyrus, left lingual gyrus, and left middle temporal gyrus. On the other hand, studies with intact RTs in SZ patients showed two small clusters including left cingulate gyrus and left precentral gyrus. Increased RTs in SZ groups is associated with increased activation in

more regions including VLPFC (24), supplementary motor cortex (BA 4), and occipital and temporal regions. Although our single analyses showed more activated clusters for SZ>HC within studies with impaired RTs, our ALE contrast analysis didn't show significant increased activation in that contrast comparing to SZ>HC within unimpaired RTs contrast. Both contrasts showed overlapping increased activation in one VLPFC cluster (fig 2-3).

To understand which kind of mechanisms those patterns of activation are, we need to understand other aspects for those mechanisms and whether they are reactive or proactive. For understanding those mechanisms, in the next chapters we examine group's performance and its variability then we examine the BOLD response in different level of performance depending on RT data as acceptable criteria for the cognitive mechanism; proactive (fast performance) vs. reactive (slow performance). We adopted trial- to- trial approach; so we didn't have to make any assumption on the cognitive mechanism participants adopted during each trial. The only criteria we relayed on are each trial accuracy and reaction time. We assumed that correct trials with increased reaction time should reflect a compensatory mechanism (trade time for accuracy mechanism – reactive mechanism). While trials with unimpaired reaction time should reflect proactive mechanism. During the compensatory mechanism we hypothesized that participants would show greater activation in cortical regions in general and PFC in specific.

In the next chapter we are concerned with understanding how SZ patients " behaviorally" respond during the task. Do they adopt the same mechanism as HC subjects s so both groups should have similar level of variability during the task? An obvious way

to address performance variability is by examining RT data; we test performance intra-individual variability in RT data assuming increased variability would reflect different cognitive mechanism during the task.

Chapter 3 General Methods

The current sample included nineteen individuals with DSM-IV SZ; 33 siblings of individuals with SZ; 22 HC; and 28 siblings of HC subjects and the basic behavioral and fMRI task correlates were reported in previous study (Poppe et al., 2015). SZ participants were recruited from local inpatient and outpatient treatment facilities. HC subjects were recruited using local advertisements from the same community. Participants from any of the four groups were excluded if they (1) met DSM-IV criteria for substance abuse or dependence within the past 6 months; (2) had a clinically unstable or severe medical disorder, or a medical disorder that would confound the assessment of psychiatric diagnosis or render research participation dangerous; (3) had head injury (past or present) with documented neurological loss of consciousness; and (4) met DSM-IV criteria for mental retardation (mild or greater in severity). In addition, control participants as well as SZ.R were excluded if they had a lifetime history of any psychotic or major mood disorder, i.e., major depression or bipolar disorder.

Patients were evaluated using the Brief Psychiatric Rating Scale (BPRS): In addition to the total BPRS scores, we computed 3 subscales from the Brief Psychiatric Rating Scale (BPRS) as suggested by Gold et al., (2012): (1) Positive Symptoms (Grandiosity, Suspiciousness, Hallucinations, Unusual Thought Content); (2) Disorganization (Bizarre Behavior, Disorientation, Conceptual Disorganization, Mannerisms and Posturing); and (3) Negative Symptoms (Self-Neglect, Blunted Affect, Emotional Withdrawal, Motor Retardation).

Sample characteristics.

	Group				Patients vs. controls	Relatives vs. controls
	Patients	Patients' relatives	Controls	Controls' relatives		
N	19	33	22	28		
Mean age (yrs.)	26(7.7)	35(11.2)	29(7.6)	36(7.4)	$t(39) = 1.25$	$t(59) = 0.32$
% male	78.95	33.33	59.10	46.43	$\chi^2(1) = 0.28$	$\chi^2(1) = 0.84$
% Caucasian	47.37	63.64	50.00	60.71	$\chi^2(1) = 0.02$	$\chi^2(1) = 0.01$
% right handed	94.74	90.91	95.45	92.86	$\chi^2(1) = 0.48$	$\chi^2(1) = 0.07$
Education (yrs.)	13.50(2.9)	15.1(2.9)	15.6(2.0)	15.5(2.2)	$t(39) = 2.73^*$	$t(59) = 0.60$
Parental education (yrs)	15.0(2.3)	14.3(3.6)	15.1(1.6)	13.4(2.9)	$t(39) = 0.16$	$t(59) = -1.06$
Proportion of meds (atypical, other)	(.79, .21)	n/a	n/a	n/a		
BPRS	41.8	n/a	n/a	n/a		

Note: * = $p < .05$; parenthetical values following means represent standard deviations.

Fig. 3-1 *The demographic data of the current participants as published in previous study (Poppe et al., 2015)*

Behavioral Tasks

Expectancy AX-CPT The expectancy AX task is a version of the continuous performance task. The expectancy AX task includes four types of trials: AX, AY, BX and BY. AX trials are the “target trials” when a valid probe follows a valid cue. AY, BX, and BY other trial types are "non-target trials" in which a valid cue is followed by an invalid probe (AY) or an invalid cue is followed by either a generally valid (BX) or invalid probe (BY). Subjects are instructed to make one response for target trials, and another response for non-target trials. The nature of the cue (valid or invalid) provides the "context" for responding on a given trial. To encourage participants to "expect" a valid probe to follow a valid cue, the majority of trials are "target trials" (AX trials, 74%). A consequence of this manipulation is that participants develop a prepotency to respond with "target" responses on trials for which valid cues are presented, regardless of whether the trials were of the target (AX) or non-target (AY) type. Non-target cues provide the context that

a non-target response will be required, regardless of the nature of the probe - valid or invalid (Barch et al., 2001; MacDonald et al., 2003).

The current task presents 141 trials in 4 blocks of 36 trials. There are 104 AX 16 AY, 16 BX, and 8 BY trials. The cue is presented for 1000 ms, the ISI is 2000 ms, and the target is presented for 500 ms with a response window of 1500 ms. The ITI is 1200 ms. Practice trials are embedded in the task, along with instructions. Participants practiced until they obtained 80% accuracy with at least one correct 1 BX trial.

Behavioral Data analysis

Accuracy of task performance has been presented in previous work (Poppe et at., 2015). These analyses were conducted to understand a series of effects observed during accurate task performance. Cue RTs were measured when participants responded to the cues (A or B) and Probe RTs, reaction times when they responded to the probe (X or Y). Each type of reaction times was analyzed separately. Trials with reaction times below 150 were excluded from the analyses; this is often considered as an accidental key press. Original and Ex-Gaussian parameters of reaction times RT were estimated and analyzed for correct trials across all trials as well as target trials (A cues and AX probes). Target trials were chosen for two reasons: first to decrease the heterogeneity related to trial types (if any) not to RTs; second, target trails are 80 percent of the total trials, so we were still able to analyze sufficient number of trials that still represent the task.

Neuroimaging Procedures.

Subjects were administered the task in 4 blocks within one session. Functional data were collected using a 1.5 Tesla GE Sigma Scanner with the following parameters: 280 scans - repeat time (TR) of 2 s, an echo time (TE) of 40 ms, a flip angle of 90°, a voxel size of 3.4 × 3.4 × 4 mm, a field of view of 22 cm, and 24 contiguous axial slices. T1 images were collected as following: voxel size was .86×86×1.5mm thickness yielding dimensions of 256 × 256 × 124 voxels.

Neuroimaging Data Analysis

The data were preprocessed in four steps using SPM 5: the data were first slice-timing corrected. Next, realignment to the first volume in each time series was performed according to the following parameters: a 5 mm full width at half maximum (FWHM) Gaussian smoothing kernel, a 2nd degree B-spline interpolation for movement correction and a 4th degree B-spline for re-slicing. Then the data were normalized by employing an affine regularization into ICBM space, a nonlinear frequency cutoff of 25, 16 nonlinear iterations, a 4 mm3 voxel size, and a tri-linear interpolation (Poppe et al., 2015).

FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Registration to high-resolution structural and/or standard space images was carried out using FLIRT [Jenkinson 2001, 2002]. Registration from high resolution structural to standard space was then further refined using FNIRT nonlinear registration [Andersson 2007a, 2007b]. The following pre-statistics processing was applied; motion correction using MCFLIRT [Jenkinson 2002]; non-brain removal using BET [Smith 2002]; spatial

smoothing using a Gaussian kernel of FWHM 5mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=50.0s). ICA-based exploratory data analysis was carried out using MELODIC [Beckmann 2004], in order to investigate the possible presence of unexpected artifacts or activation. Z statistic images were thresholded using clusters determined by Z>2.3 and a (corrected) cluster significance threshold of P=0.01 [Worsley 2001].

In the following two chapters, we used the data collected and preprocessed as mentioned above to test our behavioral and neuroimaging hypotheses. First, we tested RT_IIV within and between groups. According to our hypothetical model, Increased RT_IIV would reflect different mechanisms under the same distribution relative to decreased RT_IIV- proactive mechanism during fast trails and reactive mechanisms during slow trials. Therefore, we hypothesized that SZ patients as well as their relatives will show increased RT_IIV during cue and probe condition. In a following study (fMRI study) we tested brain activity correlates to different level of RT to understand the nature of the underlined mechanisms.

Chapter 4 Reaction Times Intra-Individual Variability in SZ

Foreword: This chapter was written in collaboration with Angus W. MacDonald, who edited and revised versions of the manuscript.

Abstract

In the current chapter we examine reaction time intra-individual variability (RT_IIV) in SZ patients vs. HC subjects as well as within and between groups of relatives. We hypothesized that SZ patients and their relatives would exhibit increased RT_IIV that reflected the shifting of cognitive mechanisms during the same task. We applied series of Welch two sample t. tests to test groups differences in RT-IIV estimated parameters and coefficients within both conditions (cue/ probe) and across (all trials/ target trials). The findings supported our hypothesis; SZ patients showed increased RT_IIV for both condition and across all /target trials. At the same time, the increased RT_IIV in SZ patients during the cue condition was related to the overall RT means, which was not the case during the probe condition. We then tested RT_IIV coefficients' correlation to overall performance and clinical scales. the overall performance was negatively correlated to RT_IIV ex-Gaussian overall variability coefficient during the cue condition and tau for the probe condition. And both ex-Gaussian variability coefficients were positively correlated to BPRS total and positive scores.

Introduction

Ex-Gaussian Distribution.

The ex-Gaussian distributional model provides quantitative measures of the

distributional properties of reaction times for each individual. This approach assumes that the response time distribution can be modeled as the convolution of a normal distribution and an exponential distribution. It is defined by three parameters: μ (mu), the mean of the normal component, σ (sigma), the standard deviation of the normal component, and τ (tau), the slope of the exponential component. Tau – the mean of the exponential part-- provides a measure for asymmetry or skewness: A large tau refers to an increase in the tail of the probability density function (Cousineau, Brown, & Heathcote, 2004; Rentrop et al., 2010). In the current study, we applied the QMLE (Quantile Maximization Likelihood Estimation) to estimate the ex-Gaussian parameters within each subject (Cousineau et al., 2004).

Applying the QMLE, CueRTs and ProbeRTs ex-Gaussian distribution parameters (mu, sigma, and tau) were estimated for each subject separately. Previous studies estimated RT-IIV from ex-Gaussian distribution parameters by adding the component of normality "sigma" to the exponential component "tau" IIV= sigma + tau (Fassbender, Scangos, Lesh, & Carter, 2014). Although that approach represented an overall intra-individual variability estimation, some challenges are associated with this coefficient; 1. It does not differentiate between distributions with increased tau vs. others with increased sigma (Fig 4-1). For example a distribution with tau=100 and sigma=150 has the same variability of a distribution with tau=150 and sigma=100; 2. The estimated intra-individual variability is still influenced by the RTs mean. Higher RTs mean will be associated with higher IVE and vice versa.

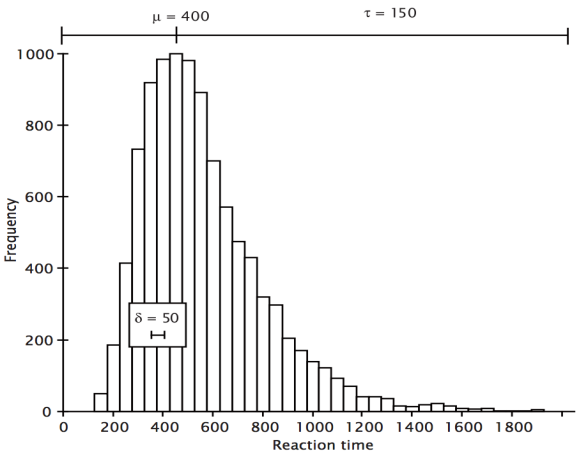


Fig. 4-1 *(Whelan ,2008). RTs distribution illustrating ex-Gaussian parameters*

Methods

To avoid reaction time data increased skewness and non-normal distribution problem, in the current study we had two different variability estimations for each RT distribution. The first estimation is the Gaussian component variability coefficient (GVC= sigma/mu). The second estimation is the overall variability coefficient (OVC= tau + sigma)/mu. Independent t-tests were performed to examine groups differences (HC vs SZ) and (HC.R vs SZ.R). To examine the relationship between RTs parameters and variability and both overall performance and clinical symptoms, we applied a stepwise regression model that included mu, tau and sigma. We also tested the two variability components separately.

Results

Subjects exhibiting less than 60% overall task performance accuracy were excluded. 22 HC, 20 SZ patients, 27 HC.R and 23 SZ relatives were included in the behavioral analysis.

General findings – RT means.

To test the differences between groups in RTs means of the correct trials we conducted t tests for both Cues and Probes conditions. Across all the correct trials for both conditions, SZ patients showed increased reaction times for cues (t [40]= 2.8, *p*= .009), and for probes (t[40]= 2.9, *p*=.009). SZ patients were also slower than HC subjects across the correct trials of the target stimuli (Table 3 and Table 4). There were no significant differences between the relatives groups.

Condition main effects and group by condition interaction effects were tested using ANOVA. The analysis showed a significant main effect for groups (F (3,37)= 15.3, *p*=.002) as well as for trial types (F(3,37)=17.2, *p*=.001, (Fig 4-2). A post hoc analysis (Tukey HSD) showed that SZ patients were significantly slower than HC. Across all subjects AY trials were significantly slower than AX and BY trials.

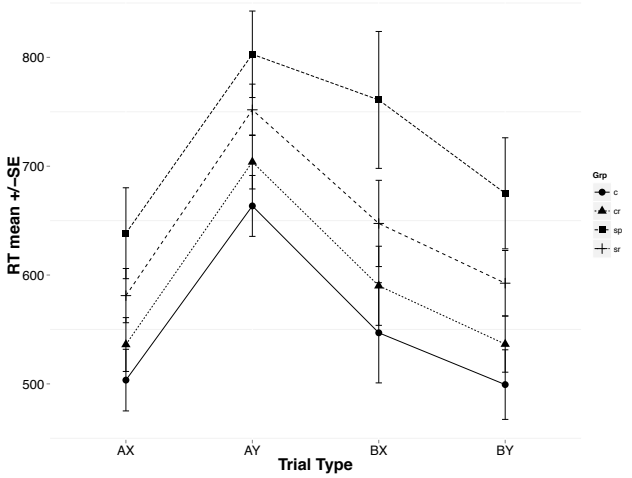


Fig. 4-2 *Probe RTs of correct trials across conditions for each group of subjects*

To control for potential differences in difficulty (and therefore accuracy) across trial types, we repeated these analyses across the correct target trials. Across the correct

target trials, SZ patients had increased reaction times for A cues (t[40] = 2.7, *p*= .01), and AX probes (t [40]= 2.7, *p*=.01). There were no significant differences between the relatives groups.

Block main effect and the group by block interaction effect were tested using repeated measure analysis (including 4 blocks). Both effects were not significant, suggesting any learning effects were negligible.

Cues Condition.

Across all the correct trials, between groups Welch two sample independent t tests were applied separately for each RT parameters. As expected, SZ patients were significantly slower than HC. They also had an increased standard deviation while the variability coefficient (VC) was not significantly different There were no significant differences between relatives groups (table 4-1). *And for the* Ex-Gaussian RT parameters. SZ patients had increased mu, sigma and IVE (tau + sigma), while they didn't show any significant differences for Tau, OVC or GVC (table 4-1 & Fig 4-3). The target trials showed similar findings unless tau was not significant (table 4-2). Replicating patients findings, SZ.R showed a trend of increased tau during all trails and trails and target trails compared to HC.R.

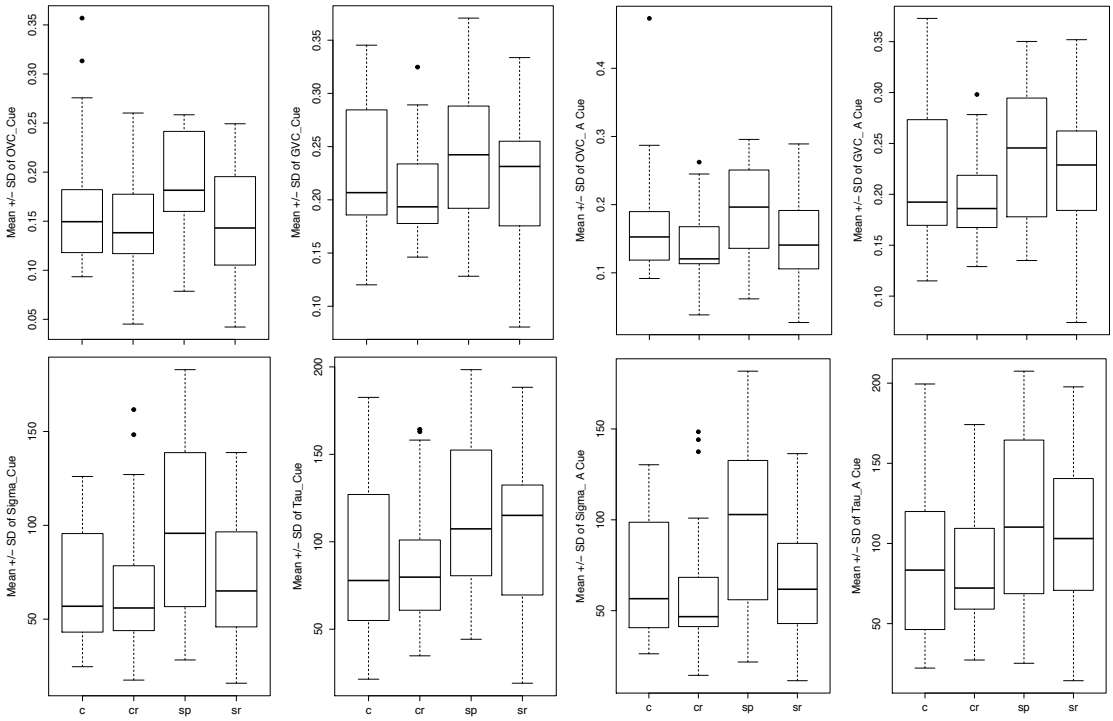


Fig. 4-3 Cue- All trials /A trials _ RT ex-Gaussian distribution's parameters within groups.

Table 4-1 Cue- All trials -RT original and ex-Gaussian distribution's parameters and RT-IIV coefficients- Groups differences (Welch independent t tests).

	SZ vs. HC		*SZ.R vs. HC.R*		
RT Parameters	*T(40)*	*P*	*RT Parameters*	*T()*	*P*
M	*2.763*	*0.009*	*M*	*0.85*	*0.399*
SD	*2.558*	*0.014*	*SD*	*1.229*	*0.224*
VC	*0.862*	*0.394*	*VC*	*0.958*	*0.342*
EX Parameters			*EX Parameters*		
Mu	*2.485*	*0.018*	*Mu*	*0.393*	*0.696*
Sig	*2.52*	*0.016*	*Sig*	*0.415*	*0.68*
Tau	*1.934*	***0.06***	*Tau*	*1.718*	*0.09*
IVE (sigma+tau)	*2.503*	*0.016*	*IVE (sigma+tau)*	*1.314*	*0.19*
GVC (sigma/mu)	*0.899*	*0.37*	*GVC (sigma/mu)*	*0.49*	*0.63*
OVC (sigma+tau)/mu	*0.522*	*0.61*	*OVC (sigma+tau)/mu*	*1.36*	*0.18*

Note: SZ schizophrenia patients HC healthy controls, SZ.R relatives of schizophrenia patients; HC.R relatives of HC, M RTs mean, SD RTs standard deviation, VC variability coefficient SD/M, IVE intra-individual variability estimation (sigma+tau), GVC Gaussian variability coefficient sigma/mu, OVC overall variability coefficient (sigma+tau)/mu. Due to the high correlation between variables, p-values are presented as uncorrected. Trends (<0.1) and significant (<.05) p values in ***bold.***

Table 4-2 Cues - A trials - RT original and ex-Gaussian distributions' parameters - Groups differences (Welch independent t tests).

	SZ vs. HC		*SZ.R vs. HC.R*		
RT Parameters	*T(40)*	*P*	*RT Parameters(57)*	*T*	*P*
M	*2.656*	*0.0**12***	*M*	*1.018*	*0.313*
SD	*2.431*	*0.**02***	*SD*	*1.577*	*0.12*
VC	*0.917*	*0.365*	*VC*	*1.45*	*0.153*
EX Parameters	*T*	*P*	*EX Parameters*	*T*	*P*
Mu	*2.347*	*0.025*	*Mu*	*0.509*	*0.613*
Sig	*2.611*	*0.013*	*Sig*	*0.662*	*0.511*
Tau	*1.718*	*0.**09***	*Tau*	*1.801*	*0.077*
IVE (sigma+tau)	*2.287*	*0.027*	*IVE (sigma+tau)*	*1.525*	*0.133*
GVC (sigma/mu)	*0.78*	*0.44*	*GVC (sigma/mu)*	*0.642*	*0.524*
OVC (sigma+tau)/mu	*0.463*	*0.646*	*EVC (sigma+tau)/mu*	*1.468*	*0.148*

Note: See Table 4-1 for description of abbreviations.

Probes Condition.

SZ patients were significantly slower than HC. They also exhibited increased standard deviations, while the variability coefficient (VC) was not significant. There were no significant differences between relatives groups (table 4-3). ***As for the*** Ex.Gaussian RT parameters***,*** SZ patients had increased mu, sigma, tau, IVE, GVC and OVC. These findings were null in relatives groups (table 4-3). Similar findings were observed for the target trials unless GVC was not significant (table 4-4). SZ.R showed increased sigma for all trials and target trials compared to HC.R. They also showed a trend of increased GVC during all trials (table 4-3).

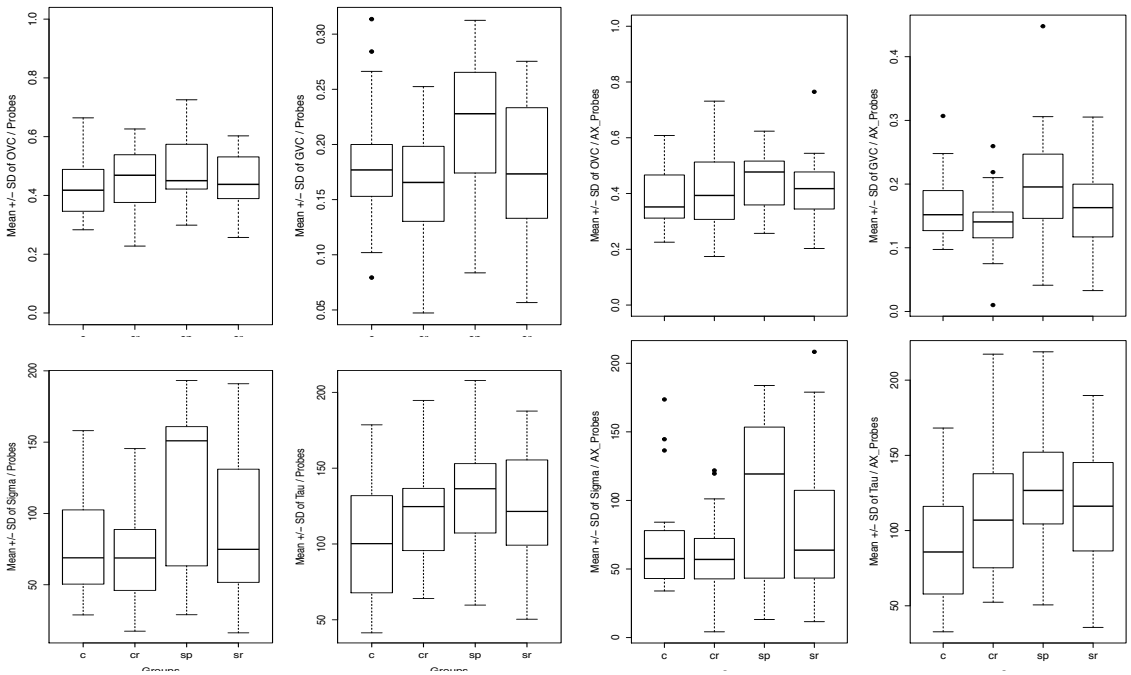


Fig. 4-4 Prob- All trials / AX trials. RT ex-Gaussian distribution's parameters within groups.

Table 4-3 Probe- all trials- RT original and ex-Gaussian distribution's parameters. Groups' differences (Welch independent t tests).

	SZ vs. HC		*SZ.R vs. HC.R*		
RT Parameters	*t( )*	*P*	*RT Parameters*	*t( )*	*P*
M	*2.808*	*0.008*	*M*	*1.227*	*0.225*
SD	*3.296*	*0.002*	*SD*	*1.41*	*0.164*
VC	*1.841*	*0.073*	*VC*	*0.678*	*0.501*
EX Parameters			*EX Parameters*		
Mu	*2.333*	*0.025*	*Mu*	*1.34*	*0.185*
Sig	*2.95*	*0.005*	*Sig*	*2.132*	*0.035*
Tau	*2.988*	*0.005*	*Tau*	*0.245*	*0.807*
IVE (sigma+tau)	*3.529*	*0.001*	*IVE (sigma+tau)*	*1.527*	*0.13*
GVC (sigma/mu)	*2.134*	*0.039*	*GVC (sigma/mu)*	*1.763*	*0.08*
OVC (sigma+tau)/mu	*2.109*	*0.041*	*OVC (sigma+tau)/mu*	*0.148*	*0.883*

Note: See Table 4-1 for description of abbreviations.

Table 4-4 Probe AX - RT original and ex-Gaussian distributions' parameters. Groups' differences (Welch independent t tests).

	SZ vs. HC		*SZ.R vs. HC.R*		
RT Parameters	*T(40)*	*P*	*RT Parameters*	*T(57)*	*P*
M	*2.675*	*0.011*	*M*	*1.241*	*0.219*
SD	*3.28*	*0.002*	*SD*	*1.141*	*0.258*
VC	*2.311*	*0.026*	*VC*	*0.285*	*0.777*
EX Parameters			*EX Parameters*		
Mu	*1.999*	*0.054*	*Mu*	*1.501*	*0.139*
Sig	*2.4*	*0.022*	*Sig*	*2.073*	*0.043*
Tau	*3.552*	*0.001*	*Tau*	*-0.008*	*0.994*
IVE (sigma+tau)	*3.426*	*0.001*	*IVE (sigma+tau)*	*1.054*	*0.296*
GVC (sigma/mu)	*1.591*	*0.121*	*GVC (sigma/mu)*	*1.431*	*0.157*
OVC (sigma+tau)/mu	*2.187*	*0.036*	*OVC (sigma+tau)/mu*	*-0.498*	*0.621*

Note: See Table 4-1 for description of abbreviations.

RT_IIV Parameters' Correlations to Clinical and Performance variables.

Multiple regression analyses were performed to test ex-Gaussian RT parameters as well as intra-individual variability coefficients correlation to the overall performance and clinical scores across all the correct trials. Analyses were performed for both cue and probe conditions across all trials. First. We tested for multicolinearity in our model using Variance Inflation Factor Analysis. Manually, we excluded one of the redundant variables until having VIF less than 3 for all variables- within probe and cue condition, VC and OVC were highly correlated, we excluded VC to have keep ex-Gaussian coefficients.

Overall performance - cue condition. In each group and across all trials, We conducted a stepwise model with accuracy percentage as the DV while group, mu, sigma and tau were predictor variables. Within SZ patients, the analysis showed significant contribution of tau [t (19) = -2.16, p=.04, R^2= .16]. Neither of the ex_Gaussian distribution parameters was related to the overall performance in HC.

A second stepwise regression model was applied to test RT_IIV coefficients contribution to the overall performance. Within both group, a Variance Inflation Factor (VIF) analysis illustrated that VC was redundant to OVC. Accordingly we excluded VC from the analysis to decrease the problem of multi-collinearity. Within SZ group, OVC showed a significant relation to the overall performance [t(19)= -2.9 . p= .009, R^2=.28]. Within HC, only IVE was significantly related to the overall performance [t(19)= -2.1, p= .048, R^2=.15].

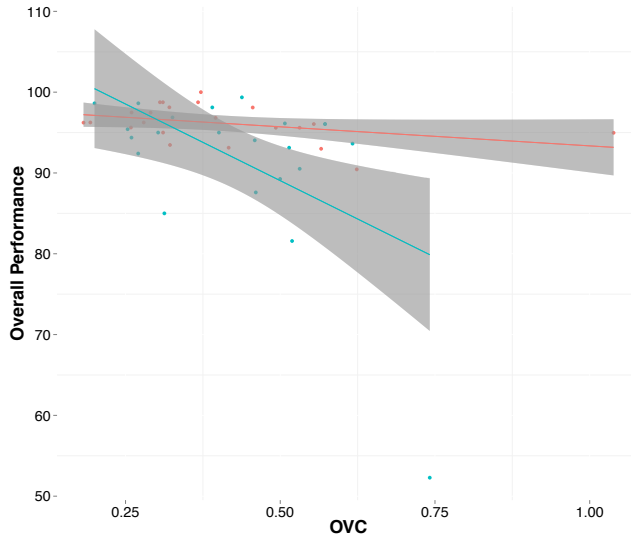


Fig. 4-5 Cue –All trials*. Scatterplot to illustrate group by OVC interaction effect on the overall performance - SZ (blue) and HC (red).*

Overall performance -probe condition. Within each group, stepwise regression analysis that included X-Gaussian parametric variables (mu, sigma, and tau) predictors and overall performance as dependent variables) was conducted. The analyses didn't show any significant contribution of ex-Gaussian parameters to the overall performance.

A second stepwise regression model was applied to test RT_IIV coefficients contribution to the overall performance. Within both group, a Variance Inflation Factor (VIF) analysis illustrated that VC was redundant to OVC. Accordingly we excluded VC from the analysis to decrease the problem of multicollinearity. There after, VIF for each included coefficients was less than 3. Only within SZ group, OVC showed a negative trend to predict the overall performance [β=-31, t (19)=-1.9, p=.07, , R^2= .13].

Clinical scores- cue condition. Across all trails, stepwise analyses were conducted with BPRS total score and sub-scores as DVs, while group, mu, sigma and tau

were the predictor variables. Only tau show a trend to predict the positive score [t(17)=2.2, p=.07, R^2=.17].

We then performed correlation matrix (corrected for multiple comparison) to evaluate the relation between RT_IIV coefficients and psychiatric symptoms; BPRS positive (M = 11.5, SD = 5.2), negative (M = 7.5, SD = 2.7), and disorganization (M = 6, SD = 2.5) subscale scores, as well as total BPRS scores (M = 43.4, SD = 10.3) for SZs. BPSR overall score were positively correlated to three variables VC [t(18) = 2.9, p=.01 , r = .62], OVC [t(18) = 2.8, p=.015 , r = .59] and GVC [t(18) = 2.3, p=.03 , r = .53] and it was a trend for tau [t(18) = 2, p=.06, r = .48] , (Fig 4-5). Score of positive symptoms showed correlation to OVC [t(18) = 2.1, p=.043, r = .5]. It also show a correlation trend to VC [t (18) = 2, p=.06, r = .48] (Fig 4_6).

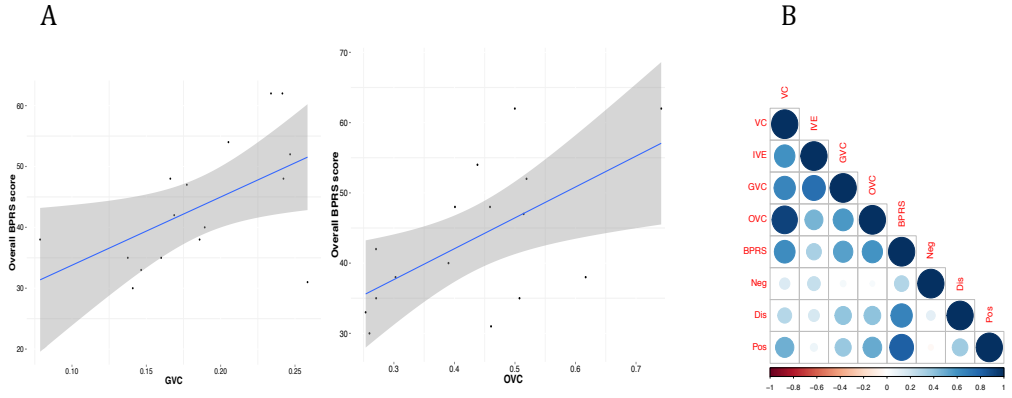


Fig. 4-6 Cue. all trials. ***A***. *BPSR overall correlation to OVC and GVC*. ***B***. *Correlation matrix between RT_IIV parameters (GVC &OVC) and BPSR total and sub-scores*.

Clinical scores- probe condition. . Stepwise regression analyses including - mu, sigma, tau as predictors and BPRS total, positive, negative and disorganization scores as dependent variables - were conducted to test combination of ex-Gaussian distribution

parameters would predict the clinical scores. Sigma and mu were show significant relation to the total score, sigma [t (19)=2.7, p=.016] and mu [t(19)=-2.6, p=.02], R^2=.15. Only mu was significant to predict the positive score [t(19)= -2.4, p= .04], while sigma showed a trend [t(17)=1.8, p=.09]. Neither of ex-Gaussian parameter significantly predicted the negative symptoms or the disorganization symptoms scores.

We performed correlation matrix (corrected for multiple comparison) to evaluate the relation between RT_IIV coefficients and the clinical symptoms. Only VC show a positive correlation (r=.57, p= .02) to the BPSR overall score. Both OVC and GVC show a trend to predict BPRS overall score (OVC [r= .39, p = .09] ; GVC [r=.33 p= .1] (Fig 4_7). RT_IIV coefficient didn't predict the other clinical scores.

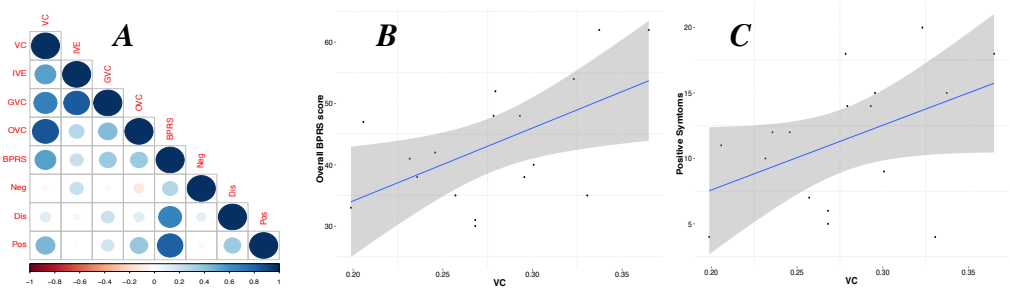


***Fig. 4-7 Probe– all trials**, **A**: Correlation matrix between RT_IIV parameters and BPSR total and sub-scores. **B.** VC correlation to BPRS overall score, **C**. VC correlation to the positive symptom score.*

Discussion

One importance of the current study is shedding light on different R_IIV variability coefficients that addressed different aspect of behavior. Beside the world wide used RT_IIV variability coefficients that introduced on previous literature -VC and IVE, (Fassbender, Lesh, et al., 2014; Kaiser et al., 2008; Rentrop et al., 2010), we presented (OVC and GVC). Both coefficients are corrected to the RT overall effect (similarly to VC coefficient), at the same time they present two different aspect of Inta- individual variability relying on the ex_Gaussian distribution. While the OVC represents the overall variability across the ex-Gaussian distribution (Gaussian + exponential data points), the GVC presents -only - the Gaussian part of the distribution excluding the exponential data points (tau). That approach of testing variability helping us understanding the source of variability within and between groups and whether its all over the performance or limited to Gaussian vs. exponential parts. As, we presented these two variables for the first time we also tested the commonly used coefficients to test our hypotheses.

Generally, and consistent with the previous reaction times literature in SZ (Rentrop et al., 2010; Vinogradov et al., 1998), patients showed decreased reaction times across all condition during all trials as well as during target trials. The findings also showed an evidence that SZ patients have increased RT-IIV in both conditions, while that variability tended to be related to the overall slowing RTs during the cue condition.

According to the current findings of the cue condition, SZ patients were slower than HC subjects and they also show increased IVE and tau (which was a trend across all trials and across target trial) but neither of RT_IIV coefficients that corrected by RTs

mean (VC, GVC and OVC) was significant. That means that the increased variability during the cue within SZ is related to the increased RTs. Also, patient's relatives had a trend of increased tau compared to HC.R. During the probe condition, SZ patients were again slower than HC. They also showed increased RT_IIV. While the increased RT_IIV variability here was represented by three RT_IIV coefficients (IIV, GVC, and OVC) across all trials and all but GVC during the target trials. One explanation for that finding is that the increased RT_IIV variability in SZ patients during the probe target (AX) condition was driven by the increased tau more than sigma. That means that SZ patients tended to have un-variant reaction time responses across the task except for the tau part of their distribution – they tended to have variant slow responses.

Interestingly, our newly presented RT_IIV coefficients (OVC / GVC) were the most repeatable correlates to the clinical scores (total and positive scores). In both conditions – across all trials – OVC and GVC coefficients were positively correlated to BPRS total and positive score.

In the next chapter, we will investigate the hemodynamic response associated with different level of RTs in both condition (cue /probe). We assumed that the increased RT-IIV in SZ would be associated with different cognitive/neural mechanisms. We hypothesized that SZ patients would have different patterns of brain activity for each RT level compared to the HC. We hypothesized that SZ patients and their relatives would have more PFC activity during the slow trials than during the faster trials relative to groups of HC.

Supplementary Analyses.

RT_IIV Parameters' Correlations to each other.

Cue Condition.

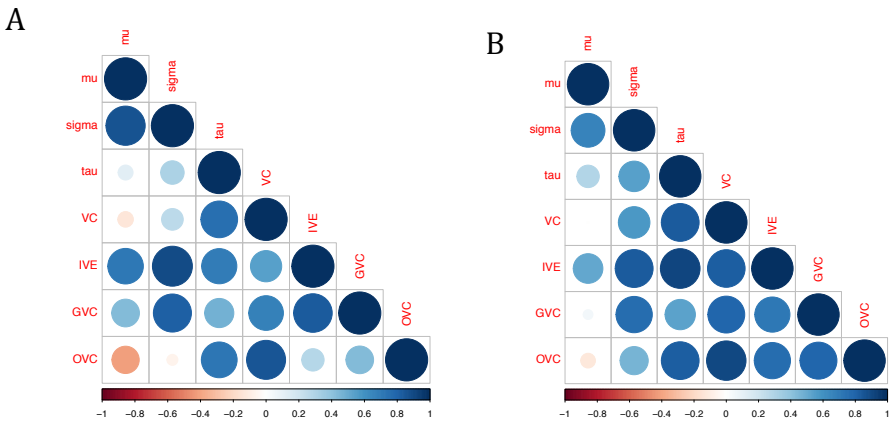


Fig. 4-8 Cue-All*- RT ex-Gaussian distribution parameters correlations within SZ (A) and HC (B)*

I tested the correlations between the estimated RT_IIV and ex-Gaussian parameters to understand the main components in each RT_IIV coefficient for each group (Fig 4-8). Fisher tests were applied to test the significance of differences between correlation coefficients of RT_IIV and variability parameters (sigma / tau) within SZ group and within HC groups. Only GVC and IVE showed similar level of correlation to tau and sigma in each group. Similarly, correlation matrix were applied in the probe condition (Fig 4-9).

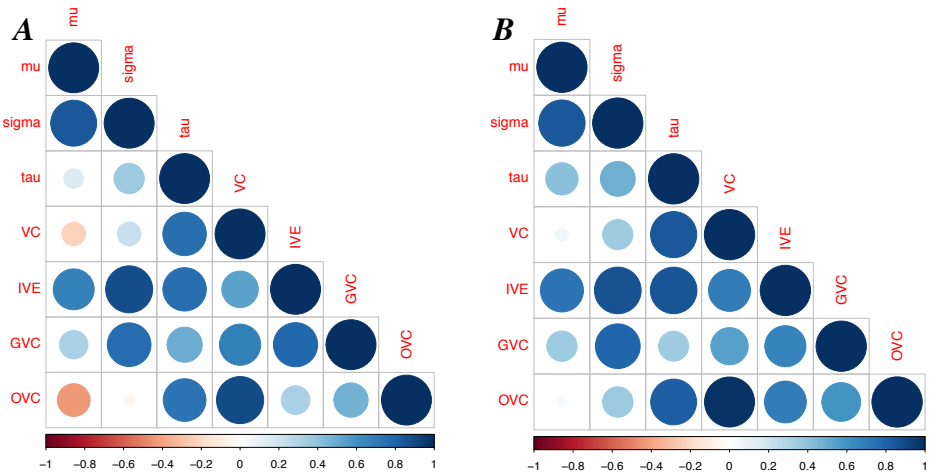


Fig. 4-9 Probe-All- RT. *ex-Gaussian distribution parameters correlations within SZ subjects (A) and HC subjects (B)*

Chapter 5 Brain activity correlates to reaction times in schizophrenia: fMRI study

Foreword: This chapter was written in collaboration with Angus W. MacDonald, who edited and revised versions of the manuscript.

Abstract

The current chapter investigated the hemodynamic response abnormalities in SZ patients associated with different levels of reaction times across the same cognitive task (AX_CPT). In general, we suggested that behavioral heterogeneity reflected by reaction times would be associated with heterogeneous neural activity.

We hypothesized that different levels of reaction times would associate with different patterns of brain activation in all groups (RT-levels main effects). We suggested that SZ patients and their relatives would have more VLPFC activity (reactive compensatory mechanisms) during the slow trials than the faster trials relative to HC, while they will have less DLPFC activity – and more motor regions activation- during the fast trials than the slow trials (motor compensatory mechanism) relative to HC. To test our hypotheses, we applied GLM to examine main and interactions effects of groups and RTs. We adopted a binning approach of RT that provides three levels of RTs: fast – medium and slow depending on a quantiles cut function. Each level was included as a separate regressor in the analyses.

Introduction

Previous studies assumed that SZ patients fail to maintain context information to guide their performance during a cognitive task (Barch et al., 2004; MacDonald & Carter,

2003). They have suggested that SZ patients rely on reactive cognitive control to compensate for a proactive deficiency (Barch & Sheffield, 2014). Parallel to these findings, a large literature has reported increased reaction time intra-individual variability (RT-IIV) in SZ patients (Fassbender, Scangos, Lesh, & Carter, 2014; Kaiser et al., 2008; Rentrop et al., 2010). Moreover, there is evidence that the increased performance IIV is characteristic of people genetically liable to SZ, (Cole, Weinberger, & Dickinson, 2011). Those findings together shed light on the importance of investigating the mechanisms that underlie this fluctuating performance and whether they relate to specific symptom dimensions. The current study adopted an integrative approach for investigating impaired as well as unimpaired compensatory neural/cognitive mechanisms in SZ and their siblings during a cognitive control task. We argued that performance variability in SZ reflected in RT-IIV (Kaiser et al., 2008; Rentrop et al., 2010; Vinogradov, Poole, Willis-Shore, Ober, & Shenaut, 1998) – may provide insight into patients' proactive, reactive or other compensatory mechanisms.

Methods

Neuroimaging Procedures.

Subjects were administered the task in 4 blocks within one session. Functional data were collected using a 1.5 Tesla GE Sigma Scanner at UC Davis Medical Center with the following parameters: 280 scans - repeat time (TR) of 2 s, an echo time (TE) of 40 ms, a flip angle of 90°, a voxel size of 3.4 × 3.4 × 4 mm, a field of view of 22 cm, and 24 contiguous axial slices. T1 images were collected as following: voxel size was .86×86×1.5mm thickness yielding dimensions of 256 × 256 × 124 voxels.

Neuroimaging data analysis. The data were preprocessed in four steps using SPM 5: the data were first slice-timing corrected. Next, realignment to the first volume in each time series was performed according to the following parameters: a 5 mm full width at half maximum (FWHM) Gaussian smoothing kernel, a 2nd degree B-spline interpolation for movement correction and a 4th degree B-spline for re-slicing. Then the data were normalized by employing an affine regularization into ICBM space, a nonlinear frequency cutoff of 25, 16 nonlinear iterations, a 4 mm3 voxel size, and a tri-linear interpolation (Poppe et al., 2015).

FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Registration to high resolution standard space images was carried out using FLIRT [Jenkinson 2001, 2002]. Registration from high resolution structural to standard space was then further refined using FNIRT nonlinear registration [Andersson 2007a, 2007b]. The following pre-statistics processing was applied; motion correction using MCFLIRT [Jenkinson 2002]; non-brain removal using BET [Smith 2002]; spatial smoothing using a Gaussian kernel of FWHM 5mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=50.0s). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by Z>2.3 and a (FW corrected) cluster significance threshold of P=0.01 [Worsley 2001].

Neuroimaging statistical analyses. For the current analysis, we adopted quantiles data binning approach. Within subjects, we divided the range of RTs data into 3 quantiles

(Fast 0-0.33, Medium 0.33-0.66, and slow 0.66-1) for the correct trials.

Within each condition, we created the "3 column" file for each RT level. A whole general linear model (GLM) included 8 regressors: Fast-Cue, Medium-Cue, Slow-Cue, Fast –Probe, Medium-Probe, Slow-Probe, Probe-Errors, Cue_Errors. Only RT regressors were included in a first level analysis. The analyses were within condition contrasts as follow: Fast-Cue vs. Slow-Cue, Fast-Cue vs. Medium-Cue, Slow-Cue vs. Medium-Cue. The same contrasts were tested in the probe condition as well.

ROIs analyses. PFC regions have been consistently implicated in cognitive control functioning (Glahn et al., 2005; Minzenberg et al., 2009a). There is evidence that Left IPL and Left ACC regions show increased activation in SZ patients compared to HC subjects (Minzenberg et al., 2009). Also, in our preliminary ALE across 90 studies, the left ACC, left IPL and left Precentral gyrus showed increased activation in SZ groups relative to healthy control groups. We suggest that those regions might reflect compensatory mechanism in SZ that could be addressed by its reaction time. In the current analyses, we will test signal change in different level of reaction times for each regions. Left IPL, left ACC and left Precentral gyrus anatomical masks obtained from Harvard-Oxford Atlas. Feat-query analyses were conducted and percent of signal change were extracted and analyzed for each ROI. Percent of signal change evaluated with repeated measures ANOVA to test the main effects of groups, level of reaction times, and groups by level of reaction times.

Series repeated measure analyses were applied group and RT main effects and group by RT interaction effect.

Whole brain analyses. Grp level analysis – Repeated measure ANOVA- were conducted for each first level contrast (GLM contrasts) to test the difference in BOLD signal change between groups across whole brain voxels. For each significant cluster, and within activated regions, following up repeated measure analyses were conducted to test RT regressors' main effect on the percent signal change within and between groups.

Results

Confirmatory Analysis.

Cues condition. Across all trials, repeated measure ANOVA showed reaction time main effects in two region of interest (IPL and Precentral gyrus; Fig 5-1& table 5-1). Post-hoc analyses (Tukey HSD) showed greater change for slow and fast relative to medium reaction time. After Bonferroni correction for multiple tests, neither the group main effect nor group by reaction time interaction effects was significant. The same findings occurred when examining target trails (Cue A) (Fig 5-1 & table 5-1). These findings were replicated in relatives groups (Fig 5-2).

Table 5-1 ROIs - Cue Condition. Repeated-Measures Analysis of Variance Effect for BOLD signal change during cue all/ cue A trials.

	SZ vs. HC						*SZ.R vs. HC.R*					
Region	*CuesAll*			*CueA*			*CuesAll*			*CueA*		
L. ACC	*F(1,40)*	*P*	*ES*	*F(1,40)*	*P*	*ES*	*F(1,57)*	*P*	*ES*	*F(1,57)*	*P*	*ES*
Grp	*1.56*	*0.22*	*0.03*	*2.25*	*0.14*	*0.03*	*5.08*	*0.09*	*0.07*	*2.45*	*0.12*	*0.07*
RT	*2.81*	*0.2*	*0.01*	*0.74*	*0.48*	*0.01*	*2.06*	*0.13*	*0.01*	*1.13*	*0.32*	*0.01*
*Grp*RT*	*0.91*	*0.41*	*0*	*0.92*	*0.4*	*0.01*	*0.6*	*0.55*	*0*	*0.4*	*0.66*	*0*
L.IPL												
Grp	*2.94*	*0.28*	*0.06*	*2.08*	*0.16*	*0.03*	*3.07*	*0.08*	*0.04*	*0.01*	*0.91*	*0*
RT	*12.17*	*0*	*0.04*	*4.58*	*0.04*	*0.03*	*15.62*	*0*	*0.04*	*8.12*	*0*	*0.04*
*Grp*RT*	*0.32*	*0.73*	*0*	*0.35*	*0.7*	*0*	*0.5*	*0.61*	*0*	*0.36*	*0.7*	*0*
L.PrecG												
Grp	*4.06*	*0.15*	*0.07*	*3.4*	*0.21*	*0.05*	*1.93*	*0.17*	*0.03*	*0.13*	*0.7*	*0.03*
RT	*9.48*	*0*	*0.04*	*5.68*	*0.01*	*0.05*	*10.52*	*0*	*0.03*	*3.7*	*0.06*	*0.03*
*Grp*RT*	*0.2*	*0.82*	*0*	*0.24*	*0.78*	*0*	*0.81*	*0.45*	*0*	*0.65*	*0.55*	*0*

Note: p-values in bold are Bonferroni-correct for 3 comparison.

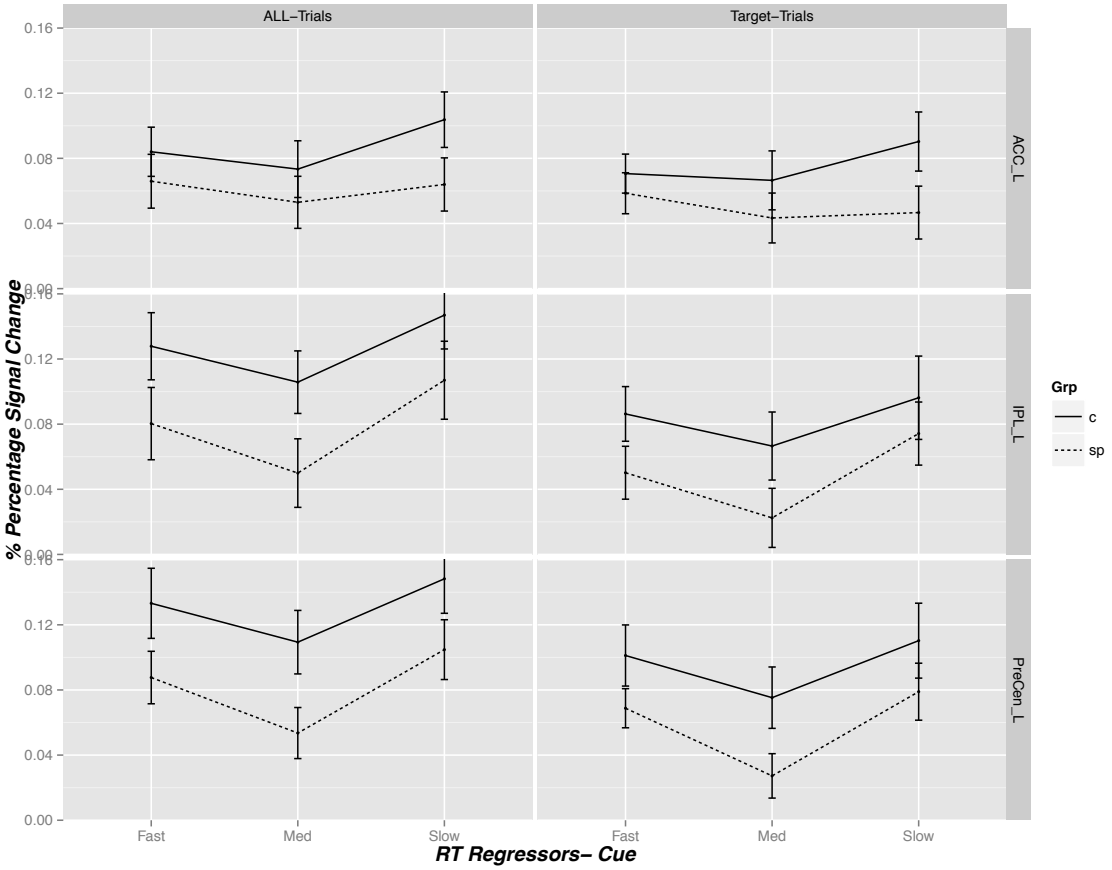


Fig. 5-1 ROIs- Cue Condition, HC vs. SZ. Percent signal changes in ACC –left side, IPL-left side and precentral gyrus –left side (as listed from up to down) across all/target trials. Note: ROIs mask were extracted from Harvard Cortical Structures Atlas.

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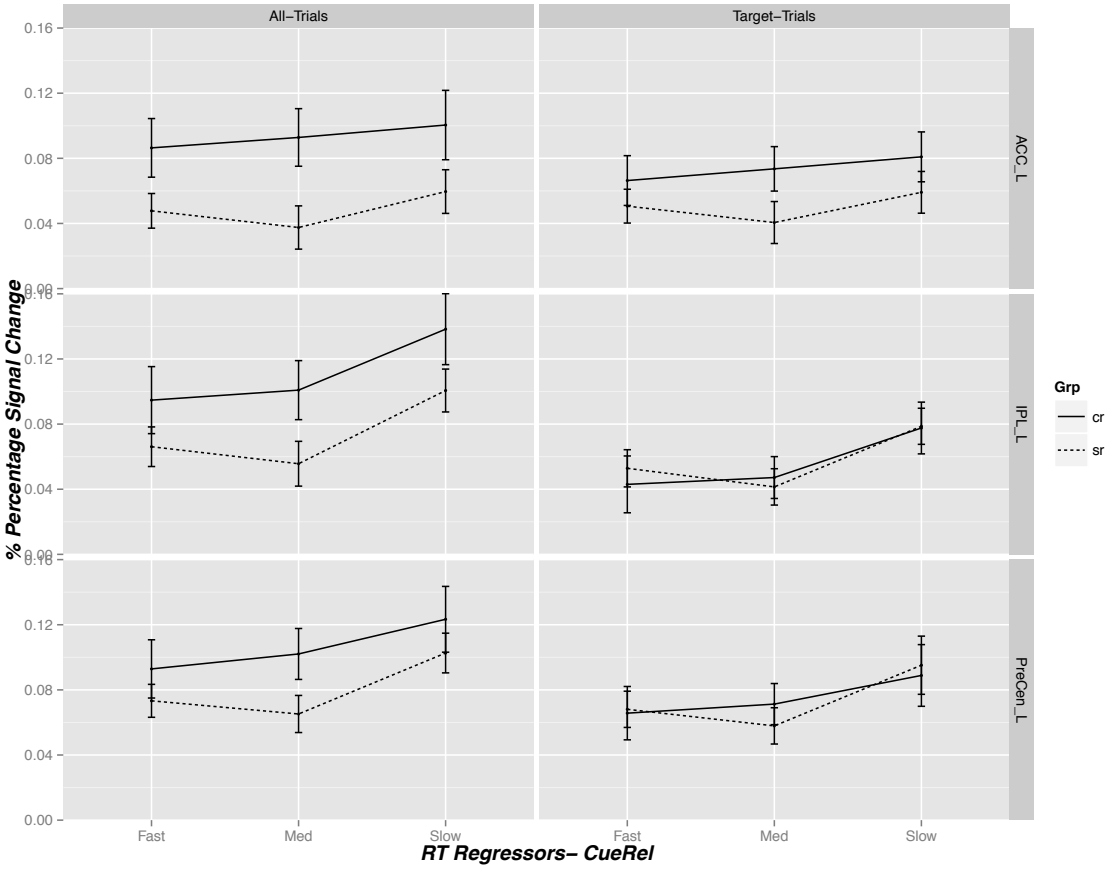

Fig. 5-2 ROIs –Cue Condition, HC.R vs SZ.R. Percent signal changes in ACC –left side, IPL-left side and precentral gyrus –left side (as listed from up to down) across all/target trials. Note: ROIs mask were extracted from Harvard Cortical Structures Atlas.

Probe Condition. Repeated measures ANOVA across all correct trials showed reaction time main effects in the three regions (ACC, IPL, and Precentral gyrus). The slow reaction time showed more signal change comparing to the medium and fast reaction time. There were no group or group by reaction time interaction effects for any regions of interest (Fig 5-3). Across the target trials (A followed by X), repeated measure ANOVA analyses revealed reaction time main effects for the three ROIs, However, group main effects and group by reaction time interaction effects were not significant for

any ROIs (table 5-2 & Fig 5-3). The findings were similar for the groups of relatives (Fig 5-4).

Table 5-2 ROIs- Probe Condition. Repeated-Measures Analysis of Variance Effect for BOLD signal change during probes and cue all/ target trials.

	SZ v. HC						*SZ.R vs. HC.R*					
Region	*Probe All*			*Probes AX*			*Probe All*			*Probes AX*		
L. ACC	*F(1,40)*	*P*	*ES*	*F(1,40)*	*P*	*ES*	*F(1,57)*	*P*	*ES*	*F(1,57)*	*P*	*ES*
Grp	*0.67*	*0.42*	*0*	*0.26*	*0.62*	*0*	*2.28*	*0.14*	*0.03*	*0.01*	*0.93*	*0*
RT	*11.86*	*0.03*	*0.06*	*4.83*	*0.03*	*0.06*	*25.25*	*0*	*0.08*	*11.13*	*0*	*0.07*
*Grp*RT*	*0.61*	*0.54*	*0.01*	*0.8*	*0.45*	*0.01*	*0.81*	*0.45*	*0*	*0.74*	*0.48*	*0*
IPL												
Grp	*1.73*	*0.28*	*0.02*	*1.34*	*0.25*	*0.02*	*1.55*	*0.22*	*0.02*	*0.71*	*0.4*	*0.01*
RT	*39.8*	*0.0*	*0.16*	*20.28*	*0*	*0.16*	*67.2*	*0*	*0.16*	*32.03*	*0*	*0.15*
*Grp*RT*	*3.05*	*0.11*	*0.05*	*0.07*	*0.93*	*0*	*0.1*	*0.9*	*0*	*0.44*	*0.65*	*0*
L. PreGy												
Grp	*1.06*	*0.31*	*0*	*0.34*	*0.56*	*0*	*0.13*	*0.72*	*0*	*3.04*	*0.09*	*0.03*
RT	*35.86*	*0.0*	*0.14*	*14.15*	*0*	*0.14*	*45.15*	*0*	*0.14*	*18.2*	*0*	*0.12*
*Grp*RT*	*1.05*	*.35*	*0*	*0.004*	*0.9*	*0*	*0.03*	*.9*	*0*	*0.97*	*0.38*	*0.01*

Note: p-values in Bold are Bonferroni-corrected for 3 comparisons.

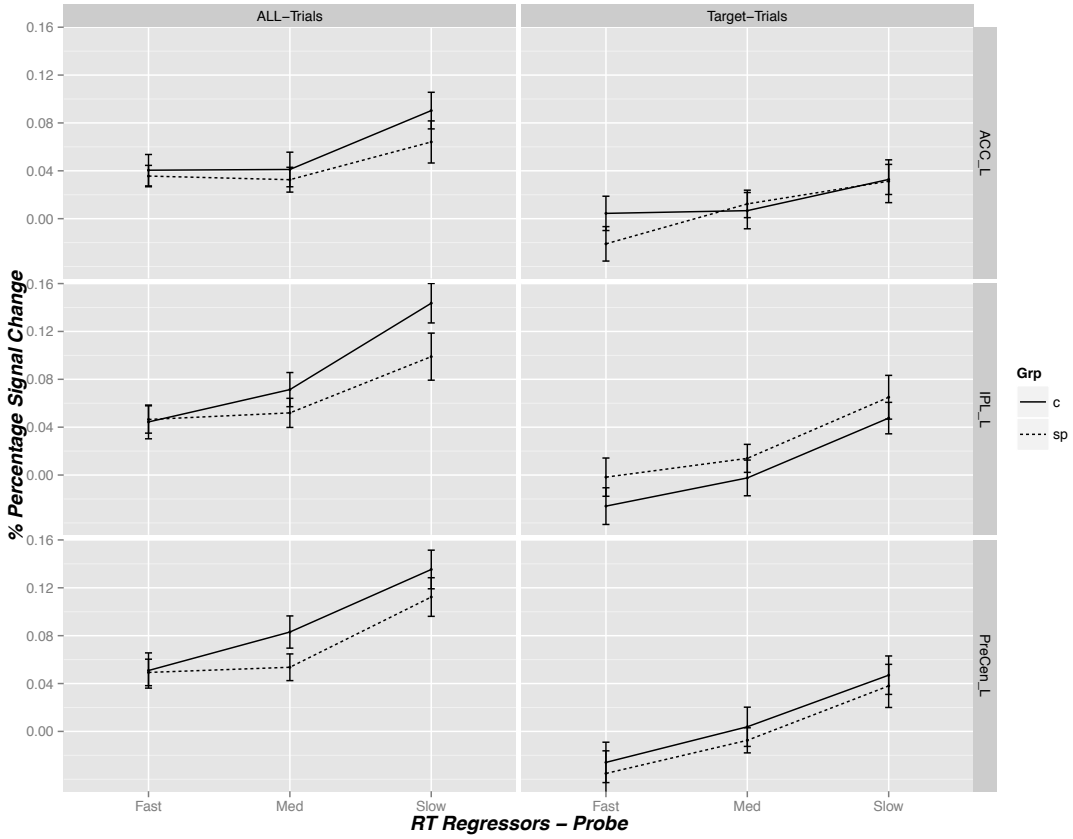

Fig. 5-3 ROIs- Probe Condition, HC vs. SZ patients. Percent signal changes in ACC – left side, IPL-left side and precentral gyrus –left side (as listed from up to down) across all/target trials. Note: ROIs mask were extracted from Harvard Cortical Structures Atlas.

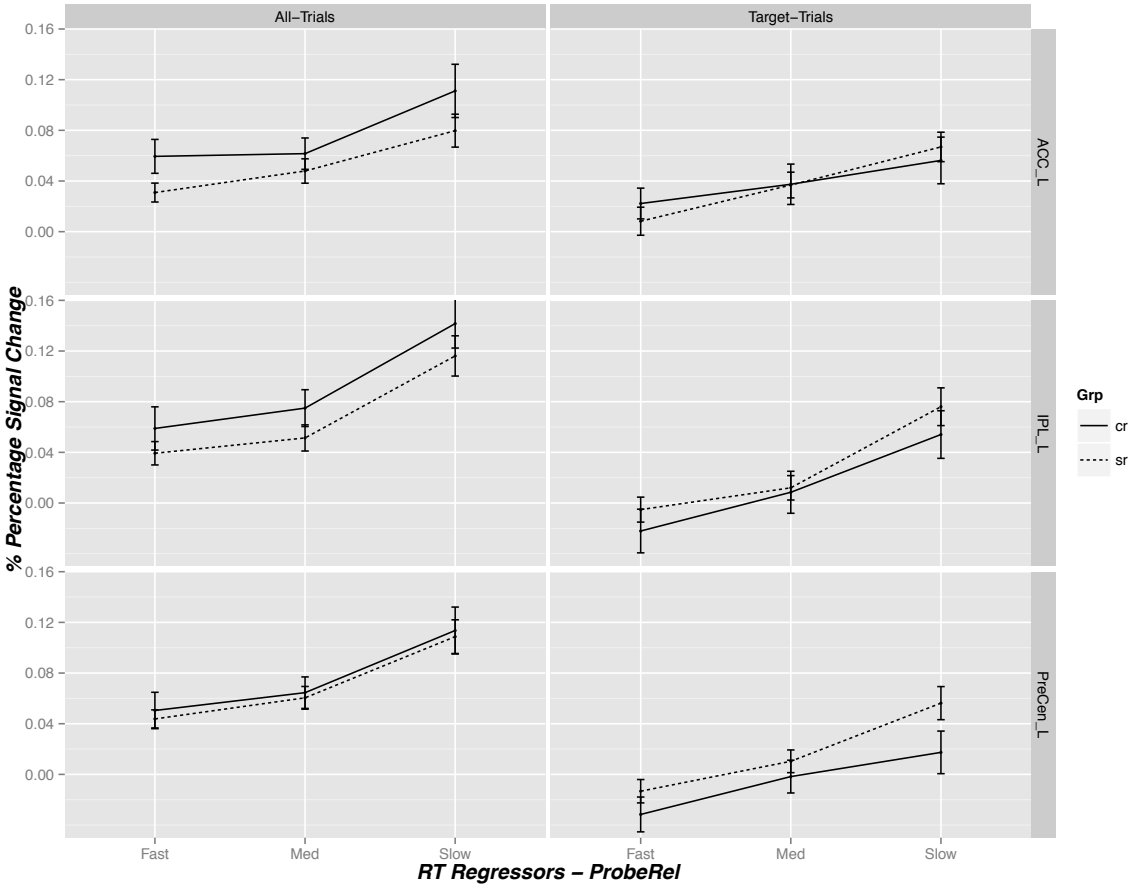

Fig. 5-4 ROIs- Probe Condition, SZ.R v. HC.R. *Percent signal changes in ACC –left side, IPL-left side and precentral gyrus –left side (as listed from up to down) across all/target trials. Note: ROIs mask were extracted from Harvard Cortical Structures Atlas.*

Exploratory Analyses.

Multiple whole brain regression analyses were applied for both probes and cues condition with the three RT regressors: (fast RT, medium RT and slow) for the correct trials of all trial types and for target trials. Group-level random-effects comparisons between the groups were computed for fast vs. medium, slow vs. medium, and medium vs. fast. All between-group contrasts were thresholded to $p < 0.01$, and clusters were

considered significant if they passed cluster-level family-wise error (FWE) correction of $p < 0.05$.

Cue condition- All trials *Within-group analysis*. All groups showed a wide rang of cortical and subcortical activation for the three levels of reaction times. In general, all groups showed increased activation during the fast performance compared to the slower performance: fast-slow, fast-medium and medium-slow. Within HC, participants had increased activation within an extended cluster for fast-slow contrast. That cluster included frontal pole, inferior parietal gyrus, precentral gyrus, postcentral gyrus, bilateral thalamus, bilateral caudate, bilateral cerebellum and a wide rang of white matter activation. HC subjects also had increased activation for the fast- medium contrast in lateral occipital cortex, frontal pole, bilateral cerebellum, right thalamus, and postcentral gyrus (table 5-3).

Similarly SZ subjects showed activation in an extended cluster for the fast–slow contrast including left cerebellum, right thalamus, and occipital fusiform gyrus. On the other hand thy showed increased signal change for the slow-medium condition that included the precentral gyrus (table 5-3). Relatives groups showed similar pattern of activation.

Table 5-3 Cues –All trials, whole brain analysis - within and between group brain activations.

HC	*size (mm^3)*	*Centroid*			*Z-max*	*Regions of activation*	*Direction*
		X	*Y*	*Z*			
Slow vs. Fast	*144631*	*-56*	*-22*	*26*	*6.79*	*L. Postcentral Gyrus,*	*F>S*
Slow vs. Medium	*7684*	*66*	*-20*	*28*	*4.4*	*R. Supramarginal gyrus, anterior division*	*M>S*
	7064	*-20*	*-90*	*-12*	*3.65*	*L. Occipital fusiform gyrus*	*M>S*

	4537	*-36*	*-40*	*22*	*4.04*	*L. Parietal Operculum Cortex*	*M>S*
Medium vs. Fast	*108777*	*48*	*-64*	*42*	*5.4*	*R. Lateral occipital cortex, superior division*	*F>M*
SZ							
Slow vs. Fast	*84678*	*-38*	*-68*	*-50*	*5.02*	*L. Cerebellum*	*F>S*
Slow vs. Medium	*3039*	*-22*	*-22*	*70*	*3.78*	*L. Precentral gyrus*	*S>M*
Medium vs. Fast	*64739*	*-40*	*-78*	*-48*	*4.99*	*L. Left cerebellum*	*F>M*
Group differences							
Slow vs. Fast	*86986*	*20*	*-26*	*12*	*4.66*	*R. Thalamus*	*F>S/ C>SZ*
	48943	*8*	*-92*	*32*	*4.14*	*R. Occipital Pole*	*F>S/ CR>SR*
Slow vs. Medium	*9965*	*-2*	*14*	*-4*	*4.45*	*L. Subcallosal cortex*	*M>S / CR>SR*

Note: HC healthy controls, SZ schizophrenia subjects, F – Fast, S – Slow , M – Medium, L – left hemisphere , R. Right hemisphere , Coordinates are reported Talairach space.

Between group analyses. HC subjects exhibited more activation change for the fast - slow contrast comparing to SZ subjects. That signal change was represented by a cluster that included postcentral gyrus, right thalamus, parietal cortex, superior longitudinal fasciculus, and callosal body (Fig 5-5). Similarly, HC.R showed a cluster of greater activation change than SZ.R for the same contrast. It included occipital pole, subcallosal cortex, superior frontal gyrus, brainstem and left cerebellum (Fig 5-6).

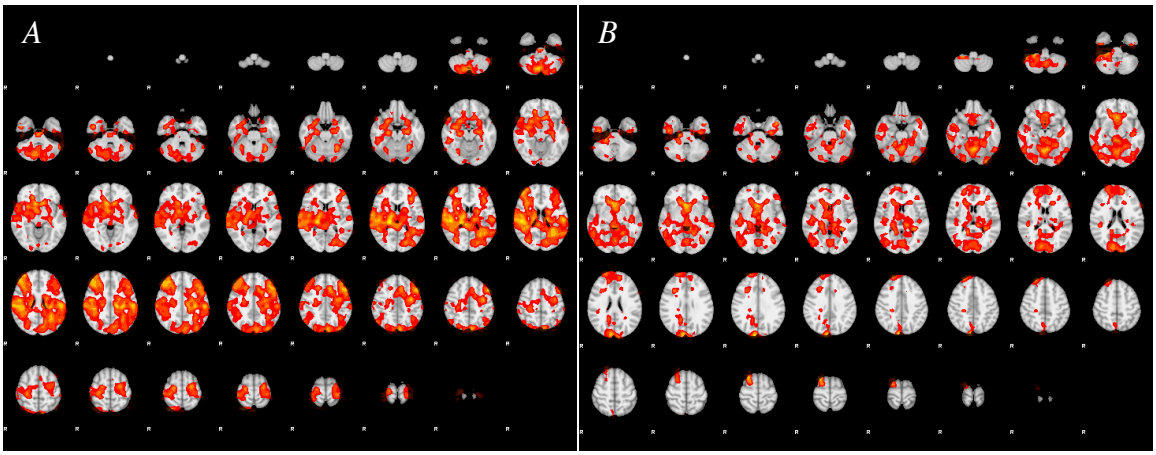

Fig. 5-5 Cue – All trials- Whole brain analysis*. Fast>slow contrast- Clusters of significant brain response that showed greater activation in HC vs. SZ subjects (A) and HC.R vs. SZ.R (B).*

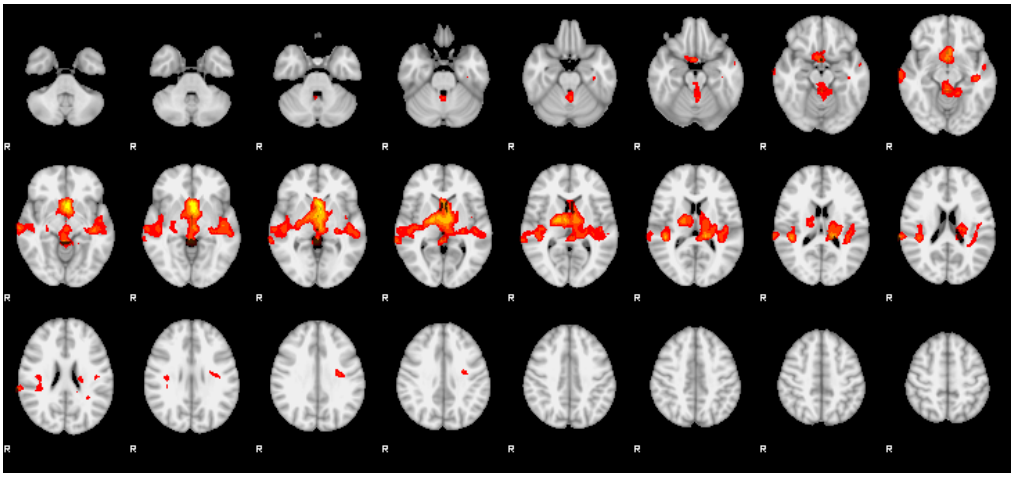

Fig. 5-6 Cue –All trials*. Medium > Slow contrast. Clusters of significant brain response showed increased activity in HC.R compared to SZ.R.*

Following up analyses were conducted. Multiple regression analyses applied to different set of activated voxels to represent specific regions of interest in the activated clusters. For doing that, we masked the activated cluster by the anatomical regions of interests' maps (created by Harvard cortical and subcortical atlases). That way, all activated voxels that didn't belong to the ROI were excluded (turned from non-zero to

zero values). We then extracted percent of signal change for the remaining voxels that belongs to the ROI. For each set of voxels (region of interest), we applied multiple regression model that included the percent signal change as a dependent variable while groups, RT-levels were the predictors. We also applied paired t test within each group as a post hoc analyses.

Bilateral MFG. Right MFG: A follow up repeated measure analysis showed significant group main effect [F (1,40)=8, p=.007] and trend RT main effect [F (1,40)=3.7, p=.06]. Group by RT effect was not significant. Post hoc paired t test analyses showed that SZ subjects significantly had increased activation during the slow trials compared to the fast trials [t (19)=-3.2, p =.004] , unlike HC subjects who had similar level of activation during fast and slow trials [t(21)=-0.4 , p =.5]. Left MFG: only group main effect was significant [F(1,40)=5.4 , p =.025]. At the same time, paired t tests showed that SZ subjects tended to have increased activation during the slow trials compared to the fast trials [t (19)=-1.8, p =.12], unlike HC subjects who had similar level of activation during fast and slow trials [t(19)=-0.2 , p =.8] _(Fig 5-7).

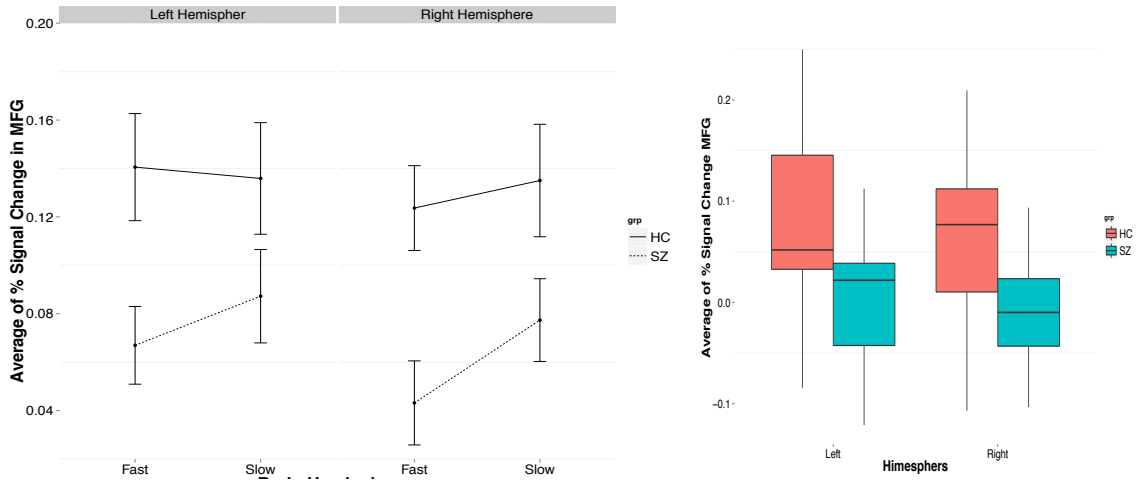

Fig. 5-7 Cue- All trials- whole brain analysis, Fast vs. slow in MFG. BOLD signal change in the activated voxels of left (L) and right (R) MFG during fast and slow trials. Right Fig. show the signal change for fast > slow in the right and the left IPL in HC and SZ. Note: significant difference "*" , trend " ^".

Bilateral IPL. Right IPL: A follow up repeated measure analysis showed significant group main effect (F (1,40)=4.4, p=.02). SZ subjects significantly had increased activation during the slow trials compared to the fast trials [t (19)=-2.6, p =.02] , while HC subjects had similar level of activation during fast and slow trials [t(19)=-0.04 , p =.9]. *Left IPL*: the analysis didn't show any significant effects. At the same time, paired t tests showed that SZ subjects significantly had increased activation during the slow trials compared to the fast trials [t (19)=-2.1, p =.04], unlike HC subjects who had similar level of activation during fast and slow trials [t(19)=-0.4 , p =.67], (Fig 5-8).

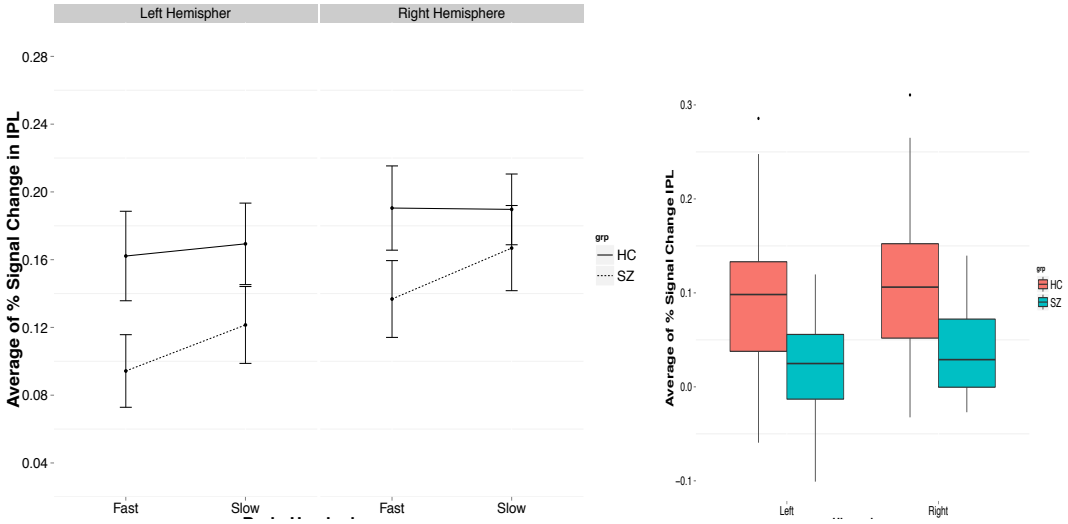

Fig. 5-8 Cue- All trials- whole brain analysis, Fast vs. slow in IPL. BOLD signal change the activated voxels of left (L) and right (R) IPL during fast and slow performance. Right Fig. Show the signal change for fast > slow in the right and the left IPL in HC subjects and SZ. Note: significant difference – stare sign "*", trend -up sign " ^".

Bilateral OFC. Right OFC: A follow up repeated measure analysis revealed no significant effects. *Left OFC*: the analysis didn't show any significant effects (Fig 5-9).

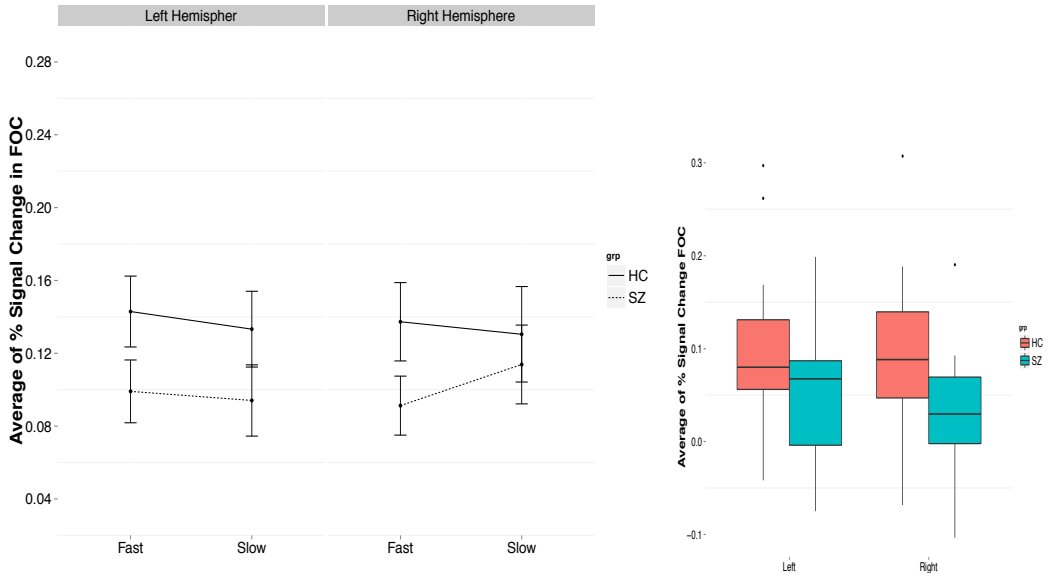

Fig. 5-9 Cue –All trials-whole brain analysis. Fast vs. slow in FOC. BOLD signal change the activated voxels of left (L) and right (R) IPL during fast and slow performance. Right Fig. show the signal change for fast > slow in the right and the left IPL in HC and SZ. Note: significant difference "*" , trend " ^".

Bilateral thalamus. Right thalamus: The follow up analysis revealed significant group main [F(1,40)= 6.9 , p=.01]. Neither RT main effect nor group by RT interaction effects was significant. Paired t tests were not significant in both groups. *Left thalamus*: the analysis revealed significant group main [F(1,40)= 6.2 , p=.016]. Neither RT main effect nor group by RT interaction effects was significant. Paired t test (fast vs. slow) were not significant in both groups (Fig 5-10).

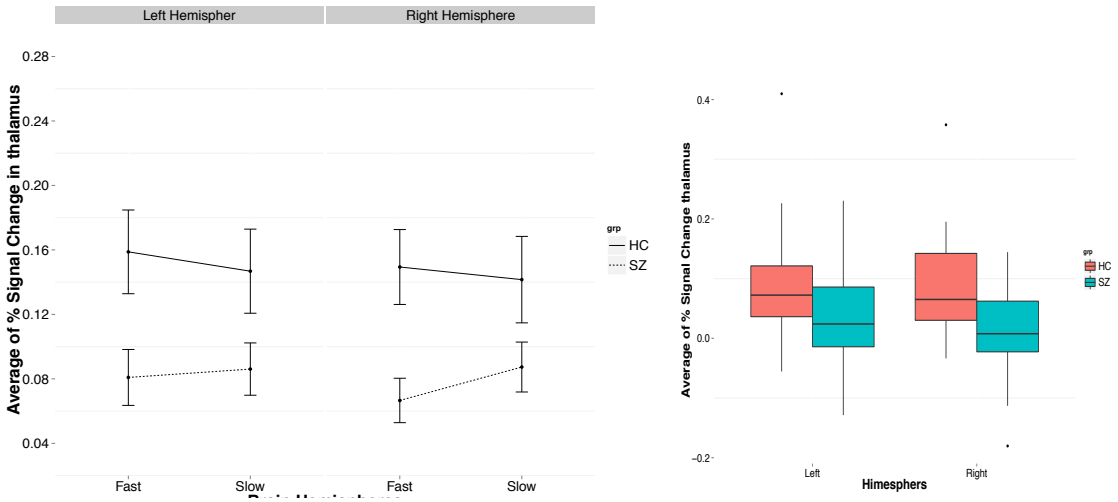

Fig. 5-10 Cue-All trials- whole brain analysis, Fast vs. slow in thalamus. BOLD signal change in the activated voxels of left (L) and right (R) thalamus. Right Fig. show the signal change for fast > slow in the right and the left thalamus in HC and SZ. Note: significant difference "*", trend " ^".

Cue condition, cue A trials. Within group analysis- RT contrasts main effects. All groups showed increased activation during the fast performance comparing to slow performance. Within HC, participants had greater activation in superior-parietal lobe, post and precentral gyrus, and frontal pole. SZ patients showed activation in different region including bilateral cerebellum and anterior thalamic radiation and lingual gyrus. Groups also had greater activation during the fast performance than the medium performance. HC subjects showed increased activation in a cluster that included precentral and postcentral gyrus, right caudate, occipital cortex, and inferior frontal gyrus. On the other hand, the slow performance yielded more activity compared to the medium performance in all groups. HC subjects and SZ subjects activated similar clusters that included supplementary motor cortex (SMC) and precentral gyrus. In HC, the same cluster also included frontal pole, cingulate gyrus and inferior frontal gyrus. Within SZ

patients it included lateral occipital cortex and postcentral gyrus (table 5-4).

Table 5-4 Cues –A - whole brain analysis - within and between group brain activations.

HC	*size (mm^3)*	*Centroid Voxel*			*Z-max*	*Regions of activation*	*Direction*
		X	*Y*	*Z*			
Slow vs. Fast	*100246*	*40*	*-44*	*70*	*5.46*	*R. Superior parietal lobule*	*F>S*
Slow vs. Medium	*14571*	*50*	*8*	*22*	*3.67*	*R. Precentral gyrus*	*S>M*
Medium vs. fast	*97344*	*24*	*20*	*32*	*4.79*	*R. Callosal body*	*F>M*
SZ							
Slow vs. Fast	*78977*	*-40*	*-64*	*-46*	*5.43*	*L. Cerebellum*	*F>S*
Slow vs. Medium	*21199*	*32*	*-22*	*78*	*4.69*		*S>M*
Medium vs. Fast	*106794*	*-14*	*-80*	*-20*	*5.2*	*L. Occipital fusiform gyrus*	*F>M*
Group Differences							
Slow vs. Fast	*13504*	*50*	*-32*	*66*	*3.65*	*L. Postcentral gyrus*	*F>S/ C>SZ*
	10509	*10*	*-94*	*34*	*4.26*	*L. Occipital Pole*	*F>S/ CR>SR*
Slow vs. Medium	*13592*	*-8*	*-32*	*8*	*3.5*	*L. Thalamus*	*M>S/ CR>SR*

Note: F – Fast, S – Slow, M – Medium, L – left hemisphere, R. Right hemisphere, Coordinates are reported Talairach space.

Between groups analysis. HC subjects exhibited more activation signal change for the Fast-slow contrast compared to SZ subjects. That change was represented by a cluster that included postcentral gyrus, right and left thalamus, right and left caudate right and left inferior parietal cortex , as well as a wide range of fronto-parital white matter activation in the left hemisphere- Superior longitudinal fasciculus. Similarly, HC.R showed a cluster of greater activation change than SZ.R for the same contrast. It included occipital pole, right cerebellum, lingual gyrus and supracalcarine cortex (table 5-4 & Fig. 5-11).

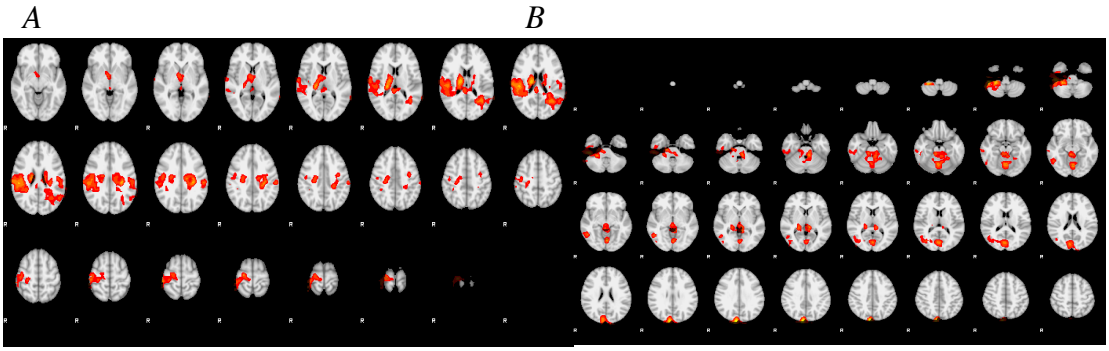

Fig. 5-11 Cue A. Fast >slow contrast. *Clusters of significant brain response that showed greater activation in HC subjects compared to SZ subjects (A) and HC.R compared to SZ.R (B).*

Bilateral IPL. Right IPL*: A follow up repeated measure analysis showed group by RT interaction effect trend (F (1,40)=2.3, p=.12) . SZ subjects tended to have increased activation during the slow trials compared to the fast trials [t (19)=-1.8, p =.1] , while HC subjects had similar level of activation during fast and slow trials;* Left IPL*: the analysis showed group by RT interaction effect trend (F(1,40)=2.5 , p=.11) . SZ subjects tended to had increase activation during the slow trials compared to the fast trials [t(19)=-1.7 , p =.12], while HC subjects had similar level of activation during fast and slow trials (Fig 5-12).*

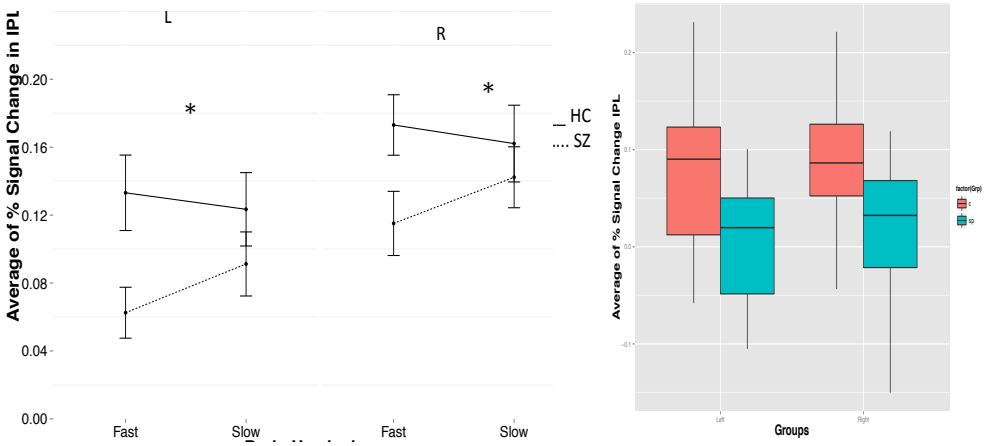

Fig. 5-12 Cue A-whole brain analysis, Fast vs. slow in IPL. BOLD signal change the activated voxels of left (L) and right (R) IPL during fast and slow performance for Cue A trials. Right Fig. show the signal change for fast > slow in the right and the left IPL in HC and SZ. Note: significant difference –stare sign "*", trend - up sign " ^".

Bilateral Thalamus. *Right thalamus*; A follow up repeated measure analysis showed group main effect [F (1,40)=5.2, p=.02]. Group by RT interaction effects was a trend [f(1,40)=2.3 , p= .11]; *Left Thalamus*: A follow up repeated measure analysis showed group and RT main effects but the interaction effect was not significant. Paired t tests showed that HC subjects tended to had more activation during the fast trials than the slow trials [t (21)= 2.2, p= .04], while SZ patients had similar level of activation during fast and slow trials [t(19)=.5 , p=.6] (Fig 5-13).

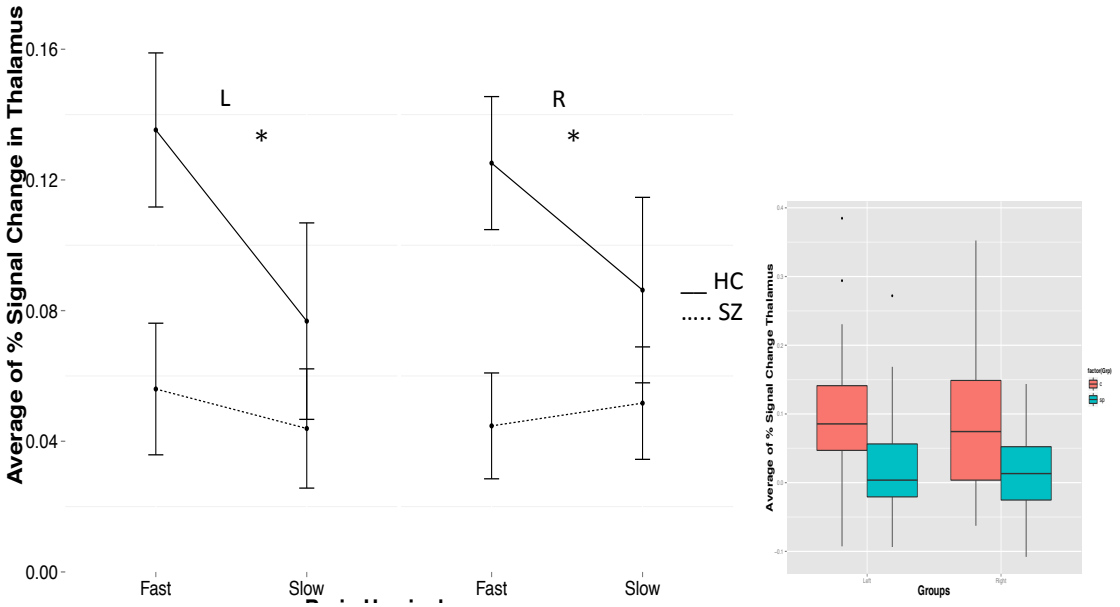

Fig. 5-13 Cue A-whole brain analysis, Fast vs. slow in thalamus. BOLD signal change the activated voxels of left (L) and right (R) thalamus during fast and slow performance for Cue A trials. Right Fig. show the signal change for fast > slow contrast in the right and the left thalamus in HC and SZ. Note: significant difference –stare sign "*, trend - up sign " ^".

Caudate. Right Caudate; A follow up repeated measure analysis showed group main effect [F (1,40)=5.4, p=.02] . Both RT main effect and group by RT interaction effects were not significant (Fig 5-15); Left Caudate: A follow up repeated measure analysis showed group by RT interaction effect trend [F (1,40)=2.4, p=.1] . Paired t tests showed that HC subjects had more activation during the fast trials than the slow trials [t (21)= 2.2, p= .04], while SZ patients had similar level of activation during fast and slow trials (Fig 5-14).

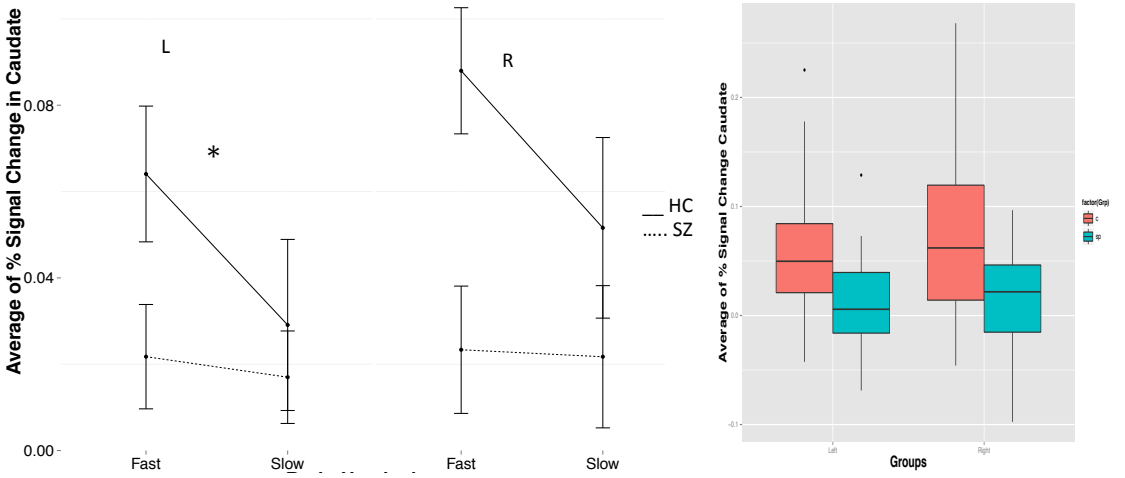

Fig. 5-14 ***Cue A-whole brain analysis, Fast vs. slow in Caudate***. BOLD signal change the activated voxels of left (L) and right (R) caudate during fast and slow performance for Cue A trials. Right Fig. show the signal change for fast > slow in the right and the left caudate in HC and SZ. Note: significant difference –stare sign "*", trend - up sign " ^".

Probes condition- all trials. With group analysis- RT contrasts main effects. All groups showed increased activation during the slow performance comparing to the fast performance (slow-fast). Within HC, participants exhibited greater activation in supplementary motor cortex (SMC), precentral gyrus and occipital pole. SZ patients showed activation in different region including precentral gyrus, middle frontal gyrus, inferior frontal gyrus, superior frontal gyrus and frontal pole. Groups also had greater white mater activation during the fast performance than the slow performance (fast-slow). HC subjects showed increased activation in a large cluster that included cortico-spinal tract, precuneous cortex, superior occipital- frontal fascicle, and cingulate gyrus. Similarly, SZ subjects showed increased activation change to fast>slow contrast

presented by a cluster of white matter coordinates. It included optic radiation, inferior occipito- frontal fascicle and left putamen. For the slow vs. medium contrasts- within HC- the slow performance yielded more activity comparing to the medium performance in two clusters of cortical regions. The first cluster included supplementary motor cortex (SMC), Precentral gyrus, superior frontal gyrus, and cingulate gyrus. The other cluster included middle temporal gyrus and lateral occipital cortex - superior division. On the other hand HC subjects showed increased activation change for (medium- slow) in two cluster including mostly white matter and subcortical regions. The first cluster included right cerebellum, right temporal occipital fusiform, right callosal body; right cortico-spinal tract and right superior occipito-frontal fascicle. The second cluster consisted of left cerebellum, left cortico-spinal tract, left callosal body, left lingual gyrus and left Superior temporal gyrus. For medium vs. fast contrast, only HC subjects showed greater activation for the medium performance. That activation was represented by one cortical cluster included precuneous cortex, lateral occipital cortex and occipital pole (table 5-5).

Table 5-5 Probe- All trials- whole brain analysis - within and between group brain activations.

HC	*size (mm^3)*	*Centroid*			*Z-max*	*Regions of activations*	*Direction*
		X	*Y*	*Z*			
Slow vs. Fast	*51061*	*2*	*6*	*60*	*5.29*	*R. Supplementary motor cortex*	*S>F*
	31088	*-24*	*-28*	*22*	*5.43*	*L. Cortico-spinal Tract*	*F>S*
Slow vs. Medium	*6899*	*-2*	*6*	*60*	*5.05*	*L. Supplementary motor cortex*	*S>M*
	3542	*-62*	*-62*	*12*	*4.6*	*L. Middle temporal gyrus, temporooccipital part*	*S>M*
	9077	*32*	*-42*	*-30*	*4.16*	*R. Cerebellum*	*M>S*
	8659	*-20*	*-30*	*26*		*L. WM Callosal body*	*M>S*

Medium vs. Fast	*10136*	*-4*	*-76*	*46*	*4.42*	*L. Precuneous Cortex*	*M>F*
SZ							
Slow vs. Fast	*11691*	*42*	*2*	*28*	*5.3*	*R. Precentral Gyrus*	*S>F*
	22267	*32*	*-16*	*-10*	*4.17*	*L. Optic radiation*	*F>S*
Slow vs. Medium		*26*	*-84*	*-24*	*4.67*	*L. Lateral occipital cortex*	*N>S*
		-30	*-66*	*-46*	*4.62*	*L. Left cerebellum*	*N>S*
Group Difference							
Slow vs. Fast	*9429*	*12*	*-102*	*24*	*3.33*	*R. Occipital Pole*	*S>F/C>SZ*
	20760	*-30*	*-20*	*16*	*4.1*	*L. Insular Cortex*	*S>F/SR>CR*

Note: F – Fast, S – Slow, M – Medium, L – left hemisphere , R. Right hemisphere , Coordinates are reported Talairach space.

Between groups analysis – Groups by RT contrasts interaction effects. HC participants exhibited more activation for the slow- fast contrast comparing to SZ subjects. A cluster that included precuneous cortex, lateral occipital cortex, superior and inferior middle temporal gyrus, temporal occipital part represented that change (Fig 5-15). Similarly, HC.R showed a cluster of greater activation change than SZ.R for the same contrast. It included insular cortex, lingual gyrus, precuneous cortex, lateral occipital cortex and cuneal cortex.

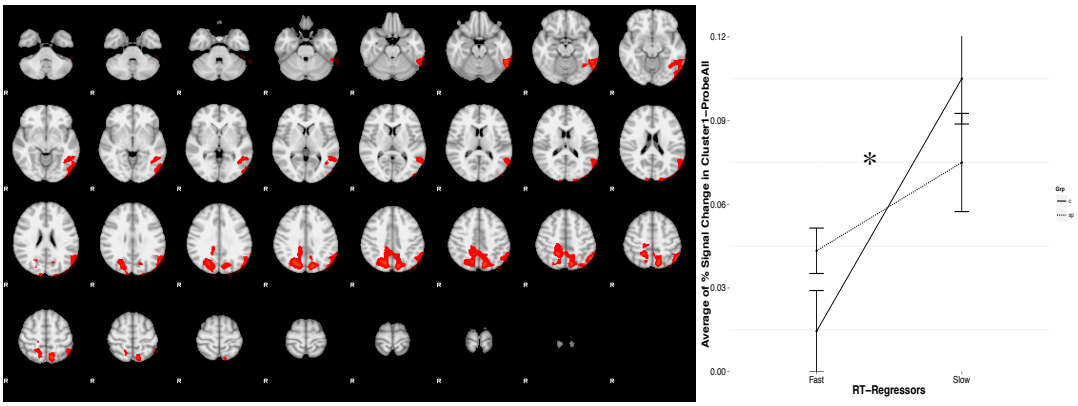

Fig. 5-15. ***Probe - All trials- whole brain anlysis, (Slow > Fast) contrast – HC>SZ.*** Cluster of significant brain response showed Increased activation change in HC > SZ patients.

Follow up analysis showed that HC subjects had more activation in that cluster during slow trials than during the fast trials relative to SZ patients.

Similarly to the cue condition, Following up analyses were conducted. Repeated measure was applied to different set of activated voxels to represent specific regions of interest in the activated clusters. Just with probe-all trials, three ROIs were tested; Precuneus cortex (medial superior parietal lobe), middle temporal gyrus (MTG) and lateral occipital gyrus (LOG). The three set of voxels showed significant RT main effect as well as group by RT interaction effects.

Bilateral Precuneus Cortex (medial superior parietal lobe)- Right side, Repeated measure analysis revealed significant RT main effect [$F(1,40)= 24.2$, $p= .001$] and significant group by RT interaction effect [$F(1,40)=6.9$, $p = .01$]. Paired t tests showed that HC subjects had more activation during the slow trials than during the fast trials [$t(21)=-5.9$, $p= .0001$] relative to SZ subjects [$t(19)=-1.4$, $p = .18$]. *Left side*, Repeated measure analyses analysis revealed significant RT main effect [$F(1,40)= 33.2$, $p= .001$] and significant group by RT interaction effect [$F(1,40)=8$, $p = .009$]. Paired t tests showed that HC subjects had more activation during the slow trials than during the fast trials [$t(21)=-6.2$, $p= .0001$] relative to SZ subjects [$t(19)=-1.1$, $p = .22$] (Fig .5-16).

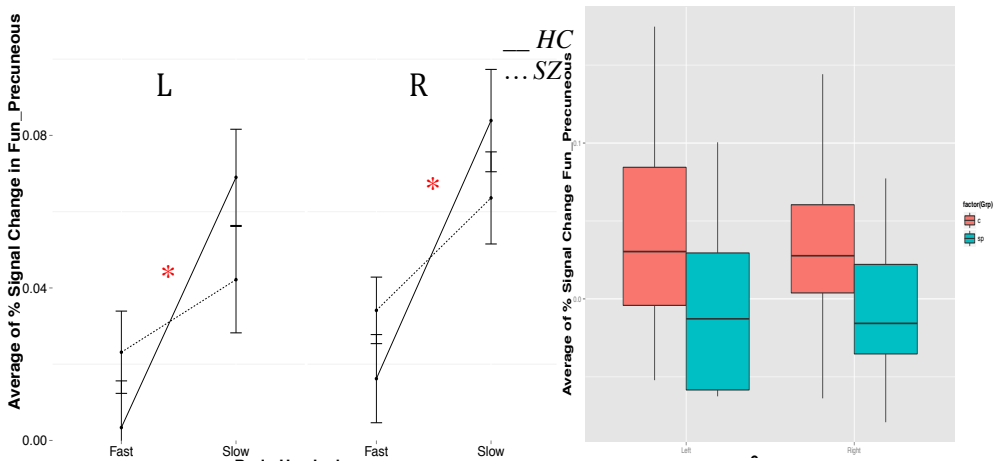

Fig. 5-16 Probe –All trials, whole brain analysis, slow vs. fast in Precuneus cortex. BOLD signal change in the activated voxels of left (L) MTG during fast and slow trials. Right Fig. show the signal change for slow > fast in the left MTG in HC (red) and SZ (blue). Note: significant difference –stare sign "*" , trend - up sign " ^".

Left MTG. Repeated measure analysis revealed significant RT main effect [F(1,40)= 37.6 , p= .003] and significant group by RT interaction effect [F(1,40)=7.8 , p = .008]. Paired t tests showed that HC subjects had more activation during the slow trials than during the fast trials [t (22)=-6.7, p= .0001] relative to SZ subjects [t(19)=-2 , p = .04], (Fig .5-17).

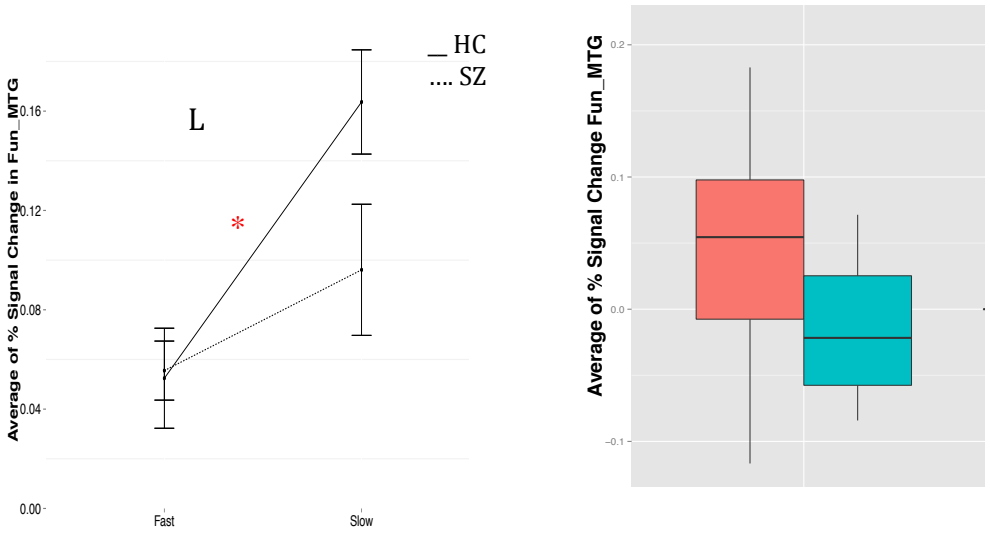

Fig. 5-17 Probe –All trials, whole brain analysis, slow vs. fast in MTG. BOLD signal change in the activated voxels of left (L) MTG during fast and slow trials. Right Fig. show the signal change for slow > fast in the left MTG in HC (red) and SZ (blue). Note: significant difference –stare sign "*", trend - up sign " ^".

Left LOG. Follow up repeated measure analysis revealed significant RT main effect [F(1,40)=13.36, p= .001] and group by reaction times interaction effect [F (1,40)=9.2 , p= .004). Paired t test analyses indicated that HC subjects significantly had more activity during the slow trials than the fast trials [t (19)= -3.3, p=.002], unlike SZ patients who had similar levels of activation for the slow and the fast trials (Fig. 5-18).

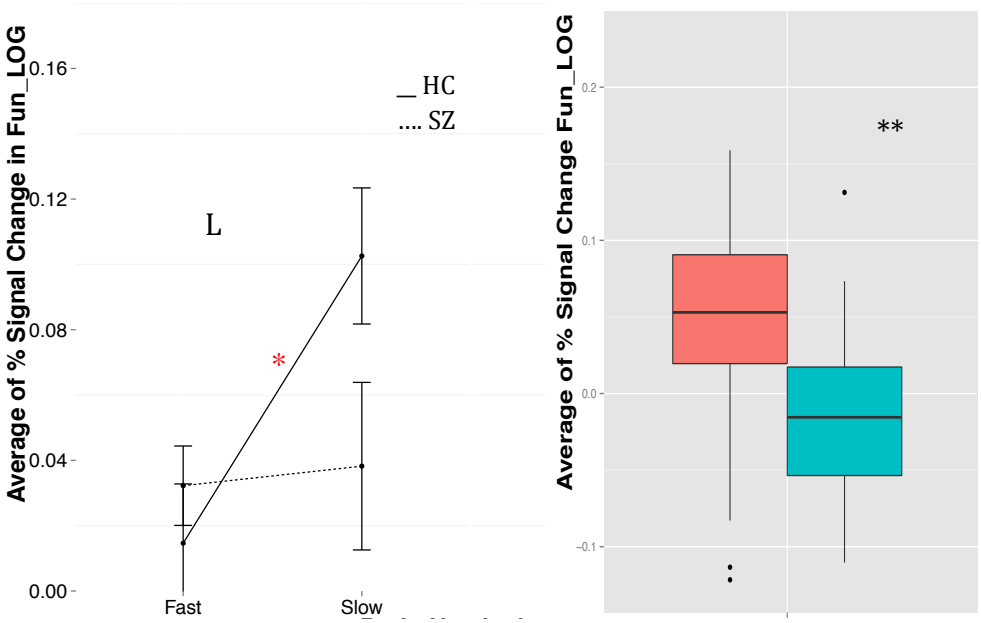

Fig. 5-18 Probe –All trials, whole brain analysis, slow vs. fast in MTG*. BOLD signal change in the activated voxels of left (L) LOG during fast and slow trials. Right Fig. show the signal change for slow > fast in the left LOG in HC (red) and SZ (blue).*

Probe condition- AX trials. Within group analysis showed that all groups had greater brain activity during the slow AX trials compared to the fast AX trials. HC subjects had increased activity in precentral gyrus, left lateral occipital gyrus, middle frontal lobe, supplementary motor area, and cuneal cortex. They also exhibited more activity during the slow trials comparing to the medium trials in supplementary motor area, precentral gyrus, cingulate gyrus, middle frontal gyrus and angular area. And during the medium trials – fast trials, they had increased activity inferior frontal gyrus, precuneus cortex, temporal pole, lateral occipital cortex, hippocampus, and frontal orbital cortex. Similarly, SZ patients activated occipital and frontal regions for the slow-fast and

slow- medium trials but they also showed increased activation in a small cluster during medium-slow trails. It included frontal orbital cortex, left pallidum, lingual gyrus, insular cortex and cortico- thalamic activation. Between groups analyses yielded increased activity in a small cluster in SZ.R comparing to HC.R for slow-medium contrast. That cluster included brain stem, frontal orbital cortex and cortico-thalamic activation (table 5-6).

Table 5-6 Probe AX- whole brain analysis - within and between group brain activations.

HC	*size (mm^3)*	*Centeroid*			*Z-max*	*Regions of activation*	*Direction*
		X	*Y*	*Z*			
Slow vs. Fast	*113341*	*-40*	*-2*	*32*	*5.23*	*L Precentral Gyrus*	*S>F*
Slow vs. Medium	*59015*	*6*	*-6*	*56*	*4.63*	*R. Supplementary Motor Cortex*	*S>M*
Medium vs. Fast	*69754*	*48*	*14*	*30*	*4.32*	*R. Inferior Frontal Gyrus*	*M>F*
SZ							
Slow vs. Fast	*108009*	*42*	*4*	*26*	*5.54*	*R. Precentral Gyrus*	*S>F*
Slow vs. Medium	*17296*	*40*	*-14*	*36*	*3.81*	*L. Precentral Gyrus*	*S>M*
	13054	*28*	*10*	*-12*	*4.13*	*R. Frontal Orbital Cortex*	*M>S*
Medium vs. Fast	*95385*	*16*	*-58*	*-4*	*4.5*	*L.*	*M>F*
		40	*24*	*18*	*4.14*	*R. Inferior Frontal Gyrus,*	
Group Difference							
Slow vs. Medium	*10228*	*0*	*-22*	*-14*	*3.69*	*L. Brain-stem, frontal orbital cortex, corico-thalamic tract.*	*S>M / SR>CR*

Note: F – Fast, S – Slow, M – Medium, L – left hemisphere, R. Right hemisphere , Coordinates are reported in Talairach space.

Discussion

Previous literature provides evidence on decreased PFC activity in SZ patients. DLPFC is the most consistent regions in these findings. At the same time, other studies showed patterns of increased PFC activity in SZ participants during cognitive performance. Increased activation in SZ suggested to be a compensatory mechanism SZ patients adopt to achieve challenging cognitive task (Minzenberg et al.,2009). Moreover, SZ cognitive performance showed increased variability relative to HC. Previous studies showed that SZ patients had increased RT variability between and within subjects (Kaiser et al., 2008; Rentrop et al., 2010; Vinogradov et al., 1998). These coincident inconsistent and variant findings of RT and brain activity shaded the light on the importance of linking both variables to each other in order to understand the underlying mechanisms.

In the current study, we adopted a binning approach to test the correlation between RT and BOLD signal change during a cognitive task (AX-CPT). We were mainly concerned with investigating whether subjects with SZ as well as HC subjects adopt different cognitive/neural mechanisms during the same task. We assumed that increased RT variability would reflect different mechanisms to each level of RT performance. As pervious studies, and our behavioral study in the current work provided an evidence on increased RT-IIV in SZ patients compared to HC subjects (Fassbender, Scangos, Lesh, & Carter, 2014; Kaiser et al., 2008; Rentrop et al., 2010), we hypothesized that SZ subjects and their relatives –unlike HC- would have significant difference of signal change between RT levels.

Consistent with previous findings of increased and intact activity in SZ, mostly

VLPFC activity (Manoach et al., 1999; Minzenberg et al., 2009b), we began with a confirmatory analyses that included three regions (left ACC, left Precentral gyrus and left inferior parietal lobe) that consistently were reported to show increased activation in SZ patients (Minzenberg et al., 2009b , Elshaikh et al.,not publised). We examined the activity in these regions at different levels of reaction time (fast, medium and slow). We hypothesized that different levels of reaction times could reflect different cognitive mechanisms that might be expressed by different patterns of brain activity in those regions. We examined two aspects of performance: RTs for cues and probes across all trials and across target trials: A cues and AX probe.

Unexpectedly, the confirmatory analyses didn't support our hypothesis that any of the three regions are involved in compensatory mechanisms SZ patients adopt to achieve the task. The groups by RT levels effects were not significant in the three regions and for each condition. However – during the probe conditions and across all trails- IPL showed a weak trend (p= .035)- that was rejected after Bonferroni correction- for HC subjects to have more activation during the slow trials than the fast trials relative to SZ patients. Similar non-statically trend was shown in the other two regions. At the same time, our milestone finding in that analyses was the significant main effects of RT-levels in both probe and cue condition and across the three regions (ACC, IPL,Precentral gyrus)- except during the cue condition, ACC was not relevant to RT levels. Regions that showed significant RT effect, are more likely to be involved in compensatory mechanism in all group. During the probe condition, subjects tend to show more activation in the slow performance compared to the fast and the medium performance. The increased activation

of the slow trials revealed a cognitive mechanism that is like to be a reactive mechanism, while decreased activation during the fast trials refers to a proactive mechanism that didn't stimulate more activation during the fast trials (Barch & Ceaser, 2012; Braver, Paxton, Locke, & Barch, 2009). That pattern of activation couldn't be attributed to the trial types (e.g. AY, BX), as the same effect was observed with AX trials. One explanation for that pattern of slow>fast activation during probe condition is: 1. Fast and accurate responses – with decreased activation- during probe condition are mainly based on efficient cueing proactive mechanism; 2. Slow and accurate responses – with increased activation- during probe condition are compensatory for failure of the proactive mechanism during cues.

On the other hand, the exploratory analyses showed group by reaction times interactions in some DLPFC and VLPC clusters. For both conditions and across both type of trials, all groups show a wide range of cortical and subcortical activity for all levels of RT. As a main effect of group, HC subjects showed increased activity than SZ patients for the three level of RT. Also healthy relatives had increased activation compared to patient's relatives the three levels across all type of trials but not across AX trial type.

Moreover, the findings supported our hypothesis during the cue condition, but not the probe condition. SZ patients showed more activation in prefrontal cortical regions, thalamus and caudate during the slow cue trials than during fast cue trials compared to HC subjects who showed similar level of activation for both regressor. Those findings were consistent with a large literature that shows more activation to cue trials as they

proactively response to the probe trials (Edwards et al 2010, Brave et al., 2012, Paxton et al, 2006). Patients were able to adopt a different compensatory mechanism to restore the context information introduced by the cues. On the other hand, our findings of the probe condition were consistent with Fassbender et al., (2014) findings that HC subjects showed more activation- mostly PFC regions- for the slow trials than the fast trials relative to SZ patients. However, we couldn't replicate these findings within target trials only. Accordingly, the way to interpret this increased activation could be overlapped between RT and trial type (AX, AY, BX, and BY) effects. Vast amount of previous literature showed more activation and increased RTs during AY and BX trial comparing to AX trials (Barch et al., 2001; Barch & Sheffeild, 2014; MacDonald et al., 2003; Poppe et al., 2015).

Finally, the findings of cue and probe conditions shed the light on a pre-prepared compensatory mechanism adopted by SZ patients during the cue condition slowing down their performance during the cue condition and enhancing their performance during the probe condition. On the other hand, unexpectedly, opposite pattern of performance were observed in HC. They showed similar level of activation during fast and slow cue trials, but they did show more activation during slow probe trials than the fast probe trials relative to SZ. That might raise a question about depending on reactive mechanisms during the challenging probe trials (AY & B X).

Chapter 6 General Discussion

Previous literature suggested that performance variability could be the key reason for the inconsistent neuroimaging findings in SZ research (Monach et al. 2003). However, between groups variability was the main concern for most studies. In the current project, we shed light on the intra-individual performance variability in SZ as a suggested reason for that inconsistency. We built our general hypothesis on the vast number of studies that showed SZ patients had increased reaction time variability during cognitive performance compared to HC subjects (Kaiser et al., 2008; Rentrop et al., 2010; Vinogradov et al., 1998). We suggested that if SZ subjects show increased performance variability for the same task and for the same cognitive demands they might adopt different mechanisms during that task.

Summary.

Three studies were conducted for addressing our hypothesis:

ALE- meta analysis (Chapter2). Summary and Conclusion

Results from the ALE meta-analysis offered an important theoretic starting point for the following studies. The main purpose of the ALE study was to determine the most consistent findings of functional neuroimaging in the SZ literature. We were concerned to extract regions that showed decreased and increased activation in SZ subjects to HC subjects suggesting that regions with increased activity would reflect a compensatory mechanisms that could be tested in the trial-to-trial approach in study 3.

A complementary purpose was to examine how studies with different RT effects would show within- and between-group differences in their patterns of activity.

Although that analysis would not serve our general hypothesis- which was mainly concerned with the intra-individual variability, it was important to examine whether increased or decreased activity in SZ could be attributed simply to groups' performance.

Consistent with previous findings, using a quantitative meta-analysis of 92 functional neuroimaging studies of executive functioning in SZ, HC groups as well as SZ groups showed a wide rang of brain activity during the cognitive tasks that mainly including the DLPFC, ACC, VLPFC, premotor cortex, lateral temporal cortical areas, parietal areas, cerebellum, and thalamus (Minzenberg et al., 2009b). Increased and decreased patterns of activation were noticed in SZ patients compared to HC. While the decreased activation could be explained as an illness manifestation, the increased patterns of activity would reflect compensatory cognitive/neural mechanisms patients adopted during the tasks. Our findings overlapped with Minzenberg (2009) finding in three regions (left ACC and left IPL and left precentral gyrus). In those regions, SZ groups showed more activation relative to HC. Furthermore, in our complimentary analyses, studies with RT effect sizes more than .03 replicated our findings as well as previous findings of increased activity in SZ groups relative to HC groups in left VLPFC, sensory-motor regions and occipital and middle temporal regions. As we expected, those findings couldn't be replicated in studies with RT effect sizes < .03. We therefore provide evidence that performance variability even across groups, revealed different patterns of brain activity in SZ patients. Depending on these findings, we moved a further step to test RT variability within subjects. We suggested that if SZ subjects had more RT intra-individual variability that might result in different pattern of brain activation across

different level of performance relative to HC.

RT intra -individual variability (Chapter 4). Summary and conclusion

As a second step and before examining trial-to-trial neuroimaging analyses, we tested RT data in SZ patients, HC subjects and relatives' groups. We were concerned with how RT data are variable within each subject and how that variability was different between groups. Beside IIV presented by Fassbender et al., (2011), we set two different coefficients: GVC and OVG that explained Gaussian distribution variability coefficient and overall distribution variability coefficients.

The results supported our hypotheses that SZ patients had increased reaction times variability for both conditions (Cue and Probe- all trials / target trials) compared to HC. However, for the cue condition RT variability in SZ patients were related to their slow performance. VC, OVC and GVC- coefficients that corrected for the RT mean- were not significant, while IIV was significantly increased in SZ patients.

Second, we examined how those increased RT variability were related to the other illness manifestations (overall performance and clinical outcomes). Interestingly, OVC and GVC for cue and probe conditions were negatively correlated to the overall performance and positively correlated to overall BPRS and positive scores. These findings indicate that increased RT variability related negatively to the overall functioning.

fMRI study Reaction Time Brain Correlates (Chapter 5)- Summary and conclusion

Consistently with our meta analysis study (study 1) and behavioral study (study 2), we directly examined cognitive /neural hypotheses related on reaction time and

accuracy. We assumed that subjects with increased RT variability might have different cognitive/neural intact/compensatory mechanisms across correct trails. We adopted trial-to-trial approach to test our hypotheses. Within subjects, RT distribution was divided into three equal parts (Fast RTs, Medium RTs, and Slow RTs). Depending on the ALE study, BOLD activity within and between groups were tested in the ACC, IPL, and Precentral gyrus. Then, for further understanding, we followed that with a whole brain analysis. Although our ROIs analysis didn't support our hypotheses of compensatory mechanisms in PFC regions, the whole brain analyses did show evidence that SZ patients adopted compensatory cognitive/neural mechanisms during the cue conditions but not the probe condition. Compared to HC, SZ patients showed more activity in MFG, IPL, thalamus and caudate regions during slow trials compared to fast trials. Similar compensatory mechanisms were also shown in SZ relatives that included only subcortical regions (thalamus and caudate).

Limitations and Future Directions

In the current fMRI study, we were able to present a quantiles binning approach that allowed us to decrease trials heterogeneity by testing each homogenous level of RTs distribution separately. We simply solving for performance heterogeneity by categorized trials according to their RTs. The RT significant main effects indicate that our approach was efficient in correlating RT to the BOLD signal change. Also, the model helps to understand different mechanisms related to specific RT performance (e.g. slow/fast). Also it is important to shed the light on some obstacle we had applying the model on a small data set. As we had to divide subjects RT distribution to three set of data (fast-

medium and slow). That is decrease the time points for each regressors relative to the common models that averaging across the entire task or across the task conditions (e.g. AX , AY, BX, BY in AX-CPT). In the current study, although it was reasonable to apply our model for each condition, the data in each condition were not enough to apply the binning approach. Accordingly we limited our analysis to a whole task analysis and target analysis (80% of the trials). Therefore, we recommend that applying the current model to multiple data sets would help us to understand more about the underlying mechanisms.

Brain connectivity – white matter activation in fast trials, across all groups, fast trials showed increased activation in a wide rang of the white matter. That might be a result of efficient brain connectivity during those trials compared to other trials. More brain connectivity studies are recommended in HC subjects as well as SZ patients to examine how brain connect during fast responses compared to slow responses. That might shed the light to understand the cognitive mechanisms of each response.

Inter-group variability

RT intra- group variability -In the current dissertation we were able to investigate different type of RT variability (inter-group and intra-individuals RT variability) in SZ in order to understand the increased inconsistency in neuroimaging literature. One other type of variability that needs to be addressed is intra-group RT variability- variability between subjects with SZ.

Error data – in our general hypothesis (page 52), we assumed efficient and inefficient cognitive /neural mechanisms. Although were able to examine for the efficient mechanism (correct trials), the error data wasn't sufficient to apply our analyses. We

recommend doing the analysis across a number of cognitive data sets.

Conclusion

The current dissertation shed the light on a different approach of cognitive analysis in SZ cognitive research. For the first time, we assumed heterogeneous performance to be associated with heterogeneous cognitive/neural mechanisms in SZ subjects. First, consistent with previous studies, we show the evidence on PFC hypo-activation in SZ patient as well as some other patterns of hyper-activation that included VLPFC regions (Precentral gyrus, anterior cingulate gyrus (ACC)), and middle occipital gyrus (MOG) and (study 1). Then, we provided and evidence on increased intra-individual variability in SZ patients (study 2).

In the current project, we provided evidence on the heterogeneity of previous neuroimaging studies in terms of whether they showed impaired vs. unimpaired RTs. Studies showed impaired RTs in SZ had extended pattern of increased activation that include (ACC, Precentral gyrus, IPL) compared to the unimpaired RT set of studies. To our knowledge, that is the first study to address performance heterogeneity- relying on RTs- in previous SZ fMRI research and could be one of the ways to solve for inconsistent neuroimaging findings in SZ.

In addition to our previous meta analyses study that gave a whole picture, we moved for a next step to test RT_IIV in SZ (Study2), and RTs within subject correlate to BOLD response (Study 3). SZ patients showed increased RT_IIV, that found to be more relative to the general slowness during the cue condition. Further, more, the pure (corrected to overall RT) RT_IIV coefficients found to be correlated negatively with the

overall performance and positively with the clinical symptoms (total and positive score). These findings shed light on whether the estimated coefficients are related to the daily functioning in SZ patients.

In our main (fMRI) study, relying on our results from the previous two studies, we tested our main hypothesis that SZ patients adopt compensatory mechanisms to achieve cognitive demands. We assumed that regions with increased activity (ALE analysis- study1), and trails with increased RT (behavioral variability- stduy2) reflected a neural compensatory mechanism. The findings provided evidence that SZ patients relied on a compensatory mechanics during the cue trails but not during the probe trails. Disagreeing with previous studies that found SZ patients to have proactive deficiency (Deanna M Barch & Ceaser, 2012; Edwards, Barch, & Braver, 2010), we suggest that SZ patients might relied on a proactive mechanism on their correct responses, but they fail when they need to shift their response (which is more likely to be reactive response). Just within probe across all trials (including AX, AY, BX and By) they show the same level of response unlike HC subjects who show increased activity for the slow trials (most likely to be AY and BX trials). Cue/probe trial-by-trial studies may provide more evidence on that hypothesis.

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Appendixes

Appendix 1

Descriptive information of the studies included in the ALE analyses (Unimpaired RT (d< .3), Impaired RT(d > .3), Not reported RT (Nr).

Note: Na- Not available, Ns-Not significant, Nr-Not reported.

Source	Task	Experiment	Group Contrasts	SZ(male)/HC(male)	Age SZ/Con	Dur-Med	% Med	SZ-RT(SD)/Con-RT(SD)	RT-Effect
Thermenos et al.,2005 -2	N-back	2-back	HC,SZ, SZ>HC, HC>SZ	71.2% / 54.3%	37.9(2.2)/37.8(2.3)	Nr	100	818.1(277.4)/821.2(149.6)	0.01
Davalos et al.,2011-2	Auditory-discrimiNrtion task	Difficult	HC>SZ	20(Nr)/20(Nr)	48.4/41.2	Nr	90	841(210)/835(273)	0.02
McAlindon et al 2008	Choice RT-Task		SZ>HC	5(5)/5(5)	39(8.8)/31(10.7)	Nr	Nr	302(49)/300.5(34)	0.05
Honey et al., 2005	CPT Task	Degraded	SZ>HC, HC>SZ	22(19)/20(18)	22(4.2)/24.7(6.4)	16.4	100	.42(.05)/.42(.06)	0.05
Bor et al.,2010-2	2-Back	Spatial	SZ>HC	22(17)/15(11)	28(7)/30(7)	Nr	Nr	505(133)/498(63)	0.06
Reiss et al., 2006-1	Choice RT task	Random	SZ,HC	10(9)/10(9)	29.1(9.4)/26.1(7.1)	Nr	Nr	415.5(77.0)/411.7(53.9)	0.06
Barch et al., 2003-2	N-Back- Verbal Non verbal	WM faces	SZ>HC, HC>SZ	38(24)/48(22)	36.5/36.3	13	100	972(254)/930(267)	0.07
Kunicki et al.,2003	Recognition task	Recognition-words	HC>SZ,SZ>HC	9(9)/9(9)	39.7(8.1)/43.2(5)	Nr	100	*t(16)=.15, p=.17*	0.07
Barch et al., 2003-1	N-Back- Verbal Non verbal	WM Words	SZ>HC, HC>SZ	38(24)/48(22)	36.5/36.3	13	100	913(316)/855(258)	0.11
Reiss et al., 2006-2	Choice RT task	Implicit Memory	HC, SZ	10(9)/10(9)	29.1(9.4)/26.1(7.1)	Nr	Nr	398.7(75.6)/389.7(55.3)	0.13
Tan et al., 2006-3	N-Back	3-Back	SZ>HC	15(15)/26(26)	32.7/32.3	Nr	100	262.7(113)/244.2(139)	0.14
Thermenos et al.,2005 -1	CPT_X		SZ>HC	71.2% / 54.3%	37.9(2.2)/37.8(2.3)	Nr	100	573.9(183.6)/552(80)	0.15
Tan et al., 2006-2	N-Back	2-Back	SZ>HC	15(15)/26(26)	32.7/32.3	Nr	100	248.4(115)/226.8(128)	0.18
Karch et al.,2009-4	N-Back		HC>SZ,SZ>HC	61(45)/61(45)	38.4(9.2)/38.8(10.1)	13(7.6)	93	545.6(373.6)/482.7(295.2)	0.19
Wang et al.,2011-2	Self other source monitoring		HC,SZ, SZ>HC, HC>SZ	23(15)/33(16)	27.3/30	Nr	Nr	1164(319)/1109(210)	0.21
Tan et al., 2004-1	MainteNrnce of Letters		HC>SZ,SZ>HC	11(5)/11(5)	25(5.5)/25.9(6.4)	Nr	100	992(34)/985(31)	0.22
Honey et al., 2005	CPT Task	None-Degrade	SZ>HC, HC>SZ	22(19)/20(18)	22(4.2)/24.7(6.4)	16.4	100	.38(.05)/.37(.04)	0.22
Barch et al., 2003-3	N-Back- Verbal Non verbal	Recog. words	SZ>HC, HC>SZ	38(24)/48(22)	36.5/36.3	13	100	1105(389)/943(241)	0.24
Wang et al.,2011-4	Self other source monitoring		HC,SZ, SZ>HC, HC>SZ	23(15)/33(16)	27.3/30	Nr	Nr	1053(276)/990(227)	0.25
Tan et al., 2004-2	Manipulation + MainteNrnce		HC>SZ,SZ>HC	11(5)/11(5)	25(5.5)/25.9(6.4)	Nr	100	994(163)/947(189)	0.27

Source	Task	Experiment	Group Contrasts	SZ(male)/HC(male)	Age SZ/Con	Dur-Med	% Med	SZ-RT(SD)/Con-RT(SD)	RT-Effect
Bor et al.,2010-1	2-Back	Verbal	SZ>HC	22(17)/15(11)	28.4(7.20/30.3(7.3)	5.5(3.9)	100	523(93)/494(64)	0.31
Eyler et al., 2004	Visual vigilance task		HC,SZ,HC>SZ,SZ>HC	9(5)/10(8)	58.9(9.9)/59.8(12.4)	33	100	575(195.37)/517.85(119.87)	0.35
Bonner-jacks et al.,2005-1	Encoding /Recognition task	Encoding	HC, SZ, HC>SZ, SZ>HC	17(15)/26(13)	21.8(2.9)/21.2(3.4)	Nr	95% - All	1139(209)/988(188)	0.35
Bonner-jacks et al.,2008-2	Incidental vs intentioNrl words	Incidental	HC, SZ, S>HC, HC>SZ	53.30%	88.20%	Nr	Nr	822(202)/719(190)*	0.35
Sabri et al., 2003	N-Back		SZ>HC	12(7)/10(6)	30.6/30.7	Nr	100	536(89)/501(99)	0.37
Spence et al., 1997-3	Oddball task		SZ>HC	7(7)/6(6)	37/38	Nr	100	600(180)/665(165)	0.37
Wang et al.,2011-3	Self other source monitoring		HC,SZ, SZ>HC, HC>SZ	23(15)/33(16)	27.3/30	Nr	Nr	908(265)/825(192)	0.37
Hashimoto et al.,2009-1	Working memory task	Visual	SZ, HC	14(13)/14(13)m	40.64(11.75)/37(11.77)	15.34(10.86)	100	1140.6(350.5)/1012.9(320.6)	0.38
Weiss et al., 2004-b	Recognition task		HC, SZ, HC>SZ, SZ>HC	15/16	46(7.4)/48(11.1)	Nr	Nr	1240(260)/1140(270)	0.38
Karch et al.,2009-3	N-Back		HC>SZ,SZ>HC	61(45)/61(45)	38.4(9.2)/38.8(10.1)	13(7.6)	93	588.9(264.9)/490.3(222.89)	0.4
Davalos et al.,2011-1	N-back		HC>SZ	20(nr)/20(nr)	48.4/41.2	Nr	90	673(195)/589(163)	0.42
Wang et al.,2011-1	Self other source monitoring		HC,SZ, SZ>HC, HC>SZ	23(15)/33(16)	27.3/30	Nr	Nr	987(283)/885(215)	0.42
Kubicki et al.,2003	Encoding task	Encoding-words	HC>SZ,SZ>HC	9(9)/9(9)	39.7(8.1)/43.2(5)	Nr	100	*t(16)=.9,p=.38*	0.45
Spence et al., 1997-4	Oddball task		SZ>HC	7(7)/6(6)	37/38	Nr	100	580(50)/614(134)	0.45
Karch et al.,2009-2	N-Back		HC>SZ,SZ>HC	61(45)/61(45)	38.4(9.2)/38.8(10.1)	13(7.6)	93	592.8(289.74)/478.3(194.2)	0.46
Bonner-jacks et al.,2008-1	Incidental vs intentioNrl words	IntentioNrl	HC, SZ, S>HC, HC>SZ	100(53.3%)	Nr	Nr	Nr	1250(142)/1090(150)	0.48
Bonner-jacks et al.,2005-2	Encoding /Recognition task	Recognition	HC, SZ, HC>SZ, SZ>HC	17(15)/26(13)	21.8(2.9)/21.2(3.4)	Nr	95% - All	1057(218)/945(238)	0.49
Barch et al., 2003-1	Visomotor		SZ, HC , SZ>HC , HC>SZ	17(8)/24(13)	36.5/36.3	Nr	100	529(82)/433(86)	0.5
Heckers et al., 2000-1	Multisource interference task	Control trials	HC,SZ	19(Nr)/15(Nr)	46.8(7.2)/46.6(9.1)	Nr	100	650(109)/603(67)	0.5
Barch et al., 2003-2	Visomotor		SZ, HC , SZ>HC , HC>SZ	17(8)/24(13)	36.5/36.3	Nr	100	550(87)/437(104)	0.51

Source	Task	Experiment	Group Contrasts	SZ(male)/HC(male)	Age SZ/Con	Dur-Med	% Med	SZ-RT(SD)/Con-RT(SD)	RT-Effect
Spence et al., 1997-1	Oddball task		SZ>HC	7(7)/6(6)	37/38	Nr	100	650(100)/603(81)	0.51
Tan et al., 2006-1	N-Back	1-Back	SZ>HC	15(15)/26(26)	32.7/32.3	Nr	100	303.5(65)/270.5(59)	0.54
Honey et al., 1999	N-Back		SZ>HC	20(20)/10(10)	37.2/38.9	12.9	100	t(18)=1.4 , p=.17	0.54
Karch et al.,2009-1	N-Back		HC>SZ,SZ>HC	61(45)/61(45)	38.4(9.2)/38.8(10.1)	13(7.6)	93	589.7(130.04)/526(97.1)	0.55
Schneider et al., 2007	N-Back		SZ>HC, HC>SZ	48(26)/57(31)	31.1(9.9)/30.9(8.3)	2 years	100	*F(1,80)=8.26 p=.01*	0.57
MacDoNrld et al., 2003	AX-CPT		HC,SZ	17(71%)17(71%)	34.2(7.7)/33.5(5.8)	Nr	100	133(146)/56(114)	0.58
Walter et al., 2003	N-Back		HC,SZ, SZ>HC, HC>SZ	15(8)/15(8)	28.7/29.8	5.5	93.33	NS F(1,29)=3.4 P=.08	0.67
Yoon et al.,2006	N-Back/ faces		HC, SZ	14(79%)/10(50%)	36.1(11.8)/30.3(7.9)	Nr	100	592(102)/520(110)	0.68
Hashimoto et al.,2009-2	Working memory task	Auditory	SZ, HC	14(13)/14(13)m	40.64(11.75)/37(11.77)	15.34(10.86)	100	1100.6(458.1)/817.5(349)	0.7
Koch et al ,2007-2	Delayed matched task		HC,SZ	13(8)/13(8)	26.2(5.4)/27.2(6.3)	Nr	all but one	781.3(141.9)/694(100.6)	0.71
Kerns et al., 2005-2	Stroop	Incongruent	SZ>HC, HC>SC	13(8)/13(9)	35.6/36	Nr	100	807.8(449.6)/567.3(150.9)	0.72
Woodward et al.,2009			SZ>HC, HC>SZ	10(2)/14(5) 15(3)/18(14)	33.5(7.5)/32(11) 22.5(3.3)/22.5(3.3)	Nr	Nr	*F(3,52)=5.5, p<.005*	0.78
Calhoun et al., 2006	Auditory Oddball		SZ>HC, HC>SZ	15(12)/15(12)	37/38	Nr	93.33	522(162.6)/431(102)	0.8
Heckers et al., 2000-2	Multisource interference task	Interference trials	HC,SZ	19(Nr)/15(Nr)	46.8(7.2)/46.6(9.1)	Nr	100	942(132)/873(79)	0.8
Spence et al., 1997-2	Oddball task		SZ>HC	7(7)/6(6)	37/38	Nr	100	677(54)/624(78)	0.8
Kerns et al., 2005-1	Stroop	Congorent	SZ>HC, HC>SC	13(8)/13(9)	35.6/36	Nr	100	609.9(215)/467(92)	0.86
Callicott et al., 2003	N-Back		SZ>HC, HC>SZ	14(11)/14(11)	31.5(8.6)/32.5(9)	Nr	100	300.9(12.4)/241.9(95.4)	0.87
Barch et al., 2003-4	N-Back- Verbal Non verbal	Recog. faces	SZ>HC, HC>SZ	38(24)/48(22)	36.5/36.3	13	100	1114(264)/198(217)	0.88
Koch et al ,2007-1	Delayed matched task		HC,SZ	13(8)/13(8)	26.2(5.4)/27.2(6.3)	Nr	All but	892.1(151.8)/779.1(102.9)	0.88
Camchong et al.,2006	DRT- Antisaccades		SZ , HC	14(7)/14(7)	37/40	Nr	Nr	366(78)/300(73)*	0.9

Source	Task	Experiment	Group Contrasts	SZ(male)/HC(male)	Age SZ/Con	Dur-Med	% Med	SZ-RT(SD)/Con-RT(SD)	RT-Effect
Johnson et al., 2006	Sequence Recall		SZ>HC, HC>SZ	18(16)/18(15)	37/37	Nr	100	.93(.12)/1.11(.24)	0.95
Wolf et al.,2009-1	Wm 3 level task	level0		16(8)/16(10)	29.6(7.2)/34.2(6.1)	Nr		773.9(146.9)/619.8(176.7)	0.95
Kaladjian et al ,2007	Go-NoGo task		SZ, HC , HC>SZ	21(19)/21(19)	34.9(9.5)	35.7(13.6)	100	398.9(61)/343.7(40.3)	1.07
Kiehl et al., 2005	Auditory Oddball task		HC, SZ, HC>SZ	18(9)/18(9)	34.8(11.1)/36.06(11.5)	NR	100	512.7(133)/377(85)	1.22
Manoach et al., 2000	Delayed Match to Sample		SZ>HC	9(7)/9(7)	42.4/38.7	25	100	*F(1,16)=7.3,P=.07*	1.3
Camchong et al.,2006	DRT			9(3)/10(2)	27.1/29.2	Nr	Nr	570(85)/441(109)	1.31
Wolf et al.,2009-4	Wm 3 level task	level3	HC,SZ HC>SZ SZ>HC	16(8)/16(10)	29.6(7.2)/34.2(6.1)	Nr	Nr	1222.1(129.9)/1028(153.8)	1.37
Wolf et al.,2009-2	Wm 3 level task	level1	HC,SZ HC>SZ SZ>HC	16(8)/16(10)	29.6(7.2)/34.2(6.1)	Nr	Nr	988.8(149.9)/762(117.6)	1.68
Ngan et al ,2003-1	Recognition Task	Speech sound	HC>SZ	14(12)/29(21)	35.1/29.3	Nr	100	652/356 / F(1,41)=26.3, p<.001	1.71
Ngan et al ,2003-2	Recognition Task	Non-speech sound	HC>SZ	14(12)/29(21)	35.1/29.3	Nr	100	695/379 / F(1,41)=26.3, p<.001	1.71
Wolf et al.,2009-3	Wm 3 level task	level2	HC,SZ HC>SZ SZ>HC	16(8)/16(10)	29.6(7.2)/34.2(6.1)	Nr	Nr	1109.9(125.3)/880.8(92)	2.08
Salgado- Pinda et al., 2004	CPT -task		HC>SZ	14(7)/14(7)	25.05(4.05)/25.14(3.32)	Nr	100	693.64(75.35)/544.35(51.09)	2.3
Mendrek et al.,2004	N-Back		HC,SZ HC>SZ SZ>HC	8(6)/8(6)	30(9)/28(8)	Nr	100	F=(1,14)=30.02 P<.001	2.9
Schlosser et al.,2009	Delayed Matching Sample task	Run1	HC>SZ,SZ>HC	13(9)/13(9)	26.4(7.6)/NR	Nr	Nr	889.2(35.6)/718.5(32.9)	4.98
Schlosser et al.,2009	Delayed Matching Sample task	Run15	HC>SZ,SZ>HC	13(9)/13(9)	26.4(7.6)/NR	Nr	Nr	797.7(29.4)/655.5(14.5)	6.2
Eyler et al., 2008	Verbal Learning: Delayed Match to		SZ>HC, HC>SZ	17(15)/14(10)	47.2/45.5	22.9	100	Nr	Nr
Fu et al., 2005	Verbal fluency task		HC>SZ	20(Nr)/11(Nr)	34.6(7.5)/30.4(6.2)	9(4)-13(9)	100	Nr	Nr
Heckers et al., 2000	Words Recognition	New-Old	HC,SZ,HC>SZ,SZ>HC	9(Nr)/8(Nr)	41.1(6.3)/42.9(4.8)	16.2(6.1)	100	Nr	Nr
		Old-New	HC,SZ,HC>SZ,SZ>HC	9(Nr)/8(Nr)	41.1(6.3)/42.9(4.8)	16.2(6.1)	100	Nr	Nr
Heinze et al.,2006	verbal learning task		HC,SZ,HC>SZ,SZ>HC	18(11)/15(10)	35.6(9)/30.5(6.8)	7.8(4.8)	100	Nr	Nr

Source	Task	Experiment	Group Contrasts	SZ(male)/HC(male)	Age SZ/Con	Dur-Med	% Med	SZ-RT(SD)/Con-RT(SD)	RT-Effect
Hofer et al.,2003-1	Recognition Memory Test	Encoding	HC,SZ,HC>SZ	10(10)/10(10)	32.5(6.4)/29.2(6.7)	76.1 Month	100	Nr	Nr
Hofer et al.,2003-2	Recognition Memory Test	Recognition	HC,SZ,HC>SZ	10(10)/10(10)	32.5(6.4)/29.2(6.7)	76.1 Month	100	Nr	Nr
Holmes et al., 2005	AX-CPT		SZ>HC, HC>SZ	7(6)/9(4)	39/34.33	Nr	0	Nr	Nr
Keedy et al., 2009	Visually Guided Saccades		SZ>HC, HC>SZ	9(6)/9(6)	t(16)=.36	Nr	Nr	Nr	Nr
Kumari et al., 2006	N-Back		SZ	36(14)/Nr	43.47/10	10	100	Nr	Nr
Laurens et al., 2003	Go/No-Go		SZ>HC	10(9)/16(12)	Not Provided	11	100	Nr	Nr
Mendrek et al., 2005	N-Back		SZ>HC, HC>SZ	12(9)/12(9)	28.75/27.75	Nr	100	Nr	Nr
Meyer-Lindenberg et al., 2001	N-Back		SZ>HC, HC>SZ	13(10)/13(10)	32.5/30.4	Nr	0	Nr	Nr
Ragland et al., 1998	Wisconsin Card Sorting		SZ>HC	15(7)/15(7)	33.5/29.6	11.1	60	Nr	Nr
Ragland et al., 2006	Recognition task			16(14)/15(13)	34.8(7.7)/32.2(7)	14.2(9)	100	Nr	Nr
Vinogradov et al.,2008	Verbal memory task	Encoding	HC,SZ, SZ>HC, HC>SZ	8(4)/8(5)	38(NR)/28(NR)	Nr	100	Nr	Nr
Vinogradov et al.,2008	Verbal memory task	Retrieval	HC,SZ, SZ>HC, HC>SZ	8(4)/8(5)	38(NR)/28(NR)	Nr	100	Nr	Nr
Weiss et al., 2003-1	Verbal memory task	Sementic	HC>SZ, SZ>HC	12(12)/12(12)	47.8(6.1)/48.8(10.5)	Nr	100	Nr	Nr
Weiss et al., 2003-2	Verbal memory task	Perceptual	HC>SZ, SZ>HC	12(12)/12(12)	47.8(6.1)/48.8(10.5)	Nr	100	Nr	Nr
Weiss et al., 2004-a	Verbal fluency		SZ , HC	9(9)/9(9)	31.4(7.3)/26.8(5.3)	4.6	100	Nr	Nr
Weiss et al., 2006	Verbal fluency		SZ, HC	7(7)/7(7)	26.6(2.5)/29.7(5.02)	Nr	Nr	Nr	Nr
Wolf et al., 2008	Auditory oddball task		SZ, HC, SZ>HC	17(53%)/21(52)	31.9(7.1)/28.6(7.1)	9.9(6.4)	100	Nr	Nr
Zierhut et al.,2010	Free recall vs Delayed recognition		HC, SZ, SZ>HC, HC>SZ	11(7)/13(6)	29/25	Nr	Nr	Nr	Nr
Zorrilla et al., 2001	Repeat task Encode task		SZ,HC, SZ>HC	9(4)/10(8)	54.4/61.9	27.3(10.6)yr	Nr	Nr	Nr
Schnell et al., 2008	Action Monitoring		SZ>HC, HC>SZ	20(20)/15(15)	30.16/30.80	Nr	20	Nr	Nr

Source	Task	Experiment	Group Contrasts	SZ(male)/HC(male)	Age SZ/Con	Dur-Med	% Med	SZ-RT(SD)/Con-RT(SD)	RT-Effect
Yoo et al., 2005	N-Back		SZ>HC, HC>SZ	10(8)/10(8)	25/23	Nr	100	Nr	Nr
Yucel et al., 2002	Stroop		SZ,HC	16(16)/15(15)	32.7/30	6.23	100	Nr	Nr
Curtis et al.,2001	Verbal & semantic decision		SZ, SZ>HC , HC>SZ	5(5)/5(5)	29.6(9.1)/31.6(3.4)	Nr	Nr	Nr	Nr
Honey et al., 2003	N-Back		SZ>HC, HC>SZ	30(27)/27(21)	36.9/35.1	13	100	Nr	Nr
Kinderman et al., 2004	Sequence Recall task		SZ>HC	10(5)/12(8)	58/63.8	21.1	100	Nr	Nr
Meisenzahl et al., 2006	N-Back		SZ>HC, HC>SZ	12(11)/12(11)	33.5/33.58	Nr	0	Nr	Nr
Perlstein et al., 2001	N-Back		HC>SZ,SZ>HC	17(11)/16(10)	36.5(7.5)/36.5(6.9)	13.9(8.4)	100	Nr	Nr
Wykes et al., 2002	N-Back		SZ>HC	6(6)/6(6)	35/36	Nr	100	Nr	Nr
Callicott et al., 2000	N-Back		SZ>HC, HC>SZ	13(10)/18(11)	33.9/29.6	10	0	Nr	Nr
Curtis et al.,1999	Verbal fluency / Semantic decision		SZ, HC , HC>SZ, SZ>HC	10(5)/10(5)	29.6/31.6	Nr	NR	Nr	Nr
Fletcher et al.,1998-1	Working memory task		SZ>HC, HC>SZ	6(6)/7(6)	Nr	> 2 yrs	100	Nr	Nr
Fletcher et al.,1998-2	Working memory task		SZ>HC, HC>SZ	6(6)/7(6)	Nr	Nr	Nr	Nr	Nr
Jansma et al., 2004	N-Back		SZ>HC	10(8)/10(8)	27.2/27.8	Nr	100	Nr	Nr
McDowell et al., 2002-1	Prosaccades		SZ>HC, HC>SZ	16(13)/14(13)	37/35	Nr	100	Nr	Nr
McDowell et al., 2002-2	Antisaccades		SZ>HC, HC>SZ	16(13)/14(13)	37/35	Nr	100	Nr	Nr
Perlstein et al., 2003-2	AX-CPT	AX-CPT	SZ>HC, HC>SZ	16(11)/15(9)	36.8/36.4	14.1	100	Nr	Nr
Rubia et al., 2001	Go/No-Go		SZ>HC, HC>SZ	6(6)/7(7)	40/40	15.7(9.8)m	100	Nr	Nr
Schlosser et al., 2003	N-Back		SZ>HC	12(11)/12(11)	33.5/33.58	4	100	Nr	Nr
Stevens et al.,1998-1	Auditory working memory	Words	SZ,HC	14(8)/14(8)	39.6(8.6)/36.8(11.8)	Nr	100	Nr	Nr
Stevens et al.,1998-2	Auditory working memory	Tone	SZ,HC	14(8)/14(8)	39.6(8.6)/36.8(11.8)	Nr	100	Nr	Nr

Source	Task	Experiment	Group Contrasts	SZ(male)/HC(male)	Age SZ/Con	Dur-Med	% Med	SZ-RT(SD)/Con-RT(SD)	RT-Effect
Weiss et al., 2003	Stroop		SZ>HC, HC>SZ	16(16)/15(15)	32.7(5.9)/30(5.6)	6.23	100	Nr	Nr
Broome et al., 2009-2	Verbal fluency		SZ>HC, HC>SZ	10(7)/15(11)	26/25	Nr	0	NS	NS
Perlstein et al., 2003-1	N-Back	N-Back	SZ>HC, HC>SZ	16(11)/15(9)	36.8/36.4	14.1	100	NS	NS
QuintaNr et al., 2003-1	Recognition task	Delayed matching of	HC,SZ, SZ>HC, HC>SZ	12(8)/12(5)	31.25(9.5)/26.8(3.8)	> 1	100	NS	NS
QuintaNr et al., 2003-2	Recognition task	Simultaneous Identity	HC,SZ, SZ>HC, HC>SZ	12(8)/12(5)	31.25(9.5)/26.8(3.8)	> 1	100	NS	NS
Ziemus et al.,2007	2-Back		HC, SZ, SZ>HC	9(5)/9(5)	46.2/44.2	Nr	100	NS P=0.97	NS
Broome et al., 2009-1	N-Back		SZ>HC, HC>SZ	10(7)/15(11)	26/25	Nr	0	NS , P=.44	NS