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ΤΜΗΜΑ ΝΟΣΗΛΕΥΤΙΚΗΣ
ΤΜΗΜΑ ΦΙΛΟΣΟΦΙΑΣ, ΠΑΙΔΑΓΩΓΙΚΗΣ ΚΑΙ ΨΥΧΟΛΟΓΙΑΣ

ΟΙΚΟΝΟΜΙΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
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«*ΒΑΣΙΚΗ ΚΑΙ ΕΦΑΡΜΟΣΜΕΝΗ ΓΝΩΣΙΑΚΗ ΕΠΙΣΤΗΜΗ*»

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Δυσλειτουργίες του κινητικοαισθητικού ελέγχου και της επεξεργασίας λήψης αποφάσεων στην σχιζοφρένεια
Dysfunctions in sensorimotor control and decision processing in schizophrenia

Thesis submitted in partial fulfillment of the requirements for the Masters' degree by the Interdepartmental Graduate Program in Cognitive Science

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Abstract

In the present study, the literature on the dysfunctions of the sensorimotor control and the processes of decision making in schizophrenia (SZ) is reviewed. At the beginning, there is an introduction with a brief description of the most characteristic symptoms of the disorder.
The anatomic presentation of the brain networks that may be lesioned in SZ follows.
Afterwards, the way decision making is taking place in health and in SZ is presented.
The next chapter presents a literature review on the sensorimotor abnormalities which are encountered in SZ. Effort was taken to combine the types of sensorimotor abnormalities with their anatomic lesions. Neurophysiological data and imaging studies were also taken into consideration.
Next, are presented the studies which have been performed using manual and saccadic reaction times, which are both known to be affected in SZ. Studies that have used manual reaction time and saccadic reaction times simultaneously are also presented.
At the end of the study there is a discussion summarizing the findings of the vast literature through the years together with suggestions for further ways of exploring the dysfunctions of the sensorimotor control and the decision making in SZ.

Σύνοψη

Στην παρούσα εργασία μελετήθηκε η βιβλιογραφία η σχετιζόμενη με την δυσλειτουργία του κινητικοαισθητικού ελέγχου και της επεξεργασίας λήψης αποφάσεων στην σχιζοφρένεια.
Αρχικά, στην εισαγωγή γίνεται μια σύντομη περιγραφή των πιο χαρακτηριστικών συμπτωμάτων της διαταραχής. Ακολουθεί η ανατομική παρουσίαση των εγκεφαλικών δικτύων που μπορεί να παρουσιάζουν βλάβη στην σχιζοφρένεια.
Κατόπιν εξετάζεται ο τρόπος επεξεργασίας της λήψης αποφάσεων σε υγιείς και σχιζοφρενείς.
Το επόμενο κεφάλαιο παρουσιάζει την βιβλιογραφία σχετικά με τις κινητικοαισθητικές ανωμαλίες που απαντώνται στην σχιζοφρένεια. Έγινε προσπάθεια να συνδεθούν οι τύποι των κινητικοαισθητικών ανωμαλιών με τις ανατομικές τους βλάβες. Επίσης ελήφθησαν υπ' όψη τα νευροφυσιολογικά δεδομένα και οι απεικονιστικές μελέτες.
Κατόπιν παρουσιάζονται οι μελέτες που έγιναν με την χρήση χειρονακτικών και σακκαδικών χρόνων αντίδρασης που και οι δύο είναι γνωστό ότι επηρεάζονται στην σχιζοφρένεια. Επίσης παρουσιάζονται μελέτες που χρησιμοποίησαν ταυτόχρονα χειρονακτικούς και σακκαδικούς χρόνους αντίδρασης.
Στο τέλος της μελέτης υπάρχει μια συζήτηση που αξιολογεί περιληπτικά τα ευρήματα της τεράστιας βιβλιογραφίας εν μέσω των ετών μαζί με υποδείξεις για περαιτέρω τρόπους διερεύνησης των δυσλειτουργιών του κινητικοαισθητικού ελέγχου και της λήψης αποφάσεων στην σχιζοφρένεια.

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Dedication

This thesis is dedicated to my family

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Thesis title

Dysfunctions in sensorimotor control and decision processing in schizophrenia

Δυσλειτουργίες του κινητικοαισθητικού ελέγχου και της επεξεργασίας λήψης αποφάσεων στην σχιζοφρένεια

INTRODUCTION

Schizophrenia (SZ)-The disease

The term SZ was first used by Bleuler (1911) to describe the syndrome that Morel has named "demence precose" (dementia praecox) (1860). Under this first name, Kraepelin (1896) made the disease known to the whole world. It was soon obvious that it was a psychotic disorder.

Characteristic symptoms

They originate from the thought disorder and the disturbances of perception, affect, sense of self and interpersonal functioning in relation to the external world.

Thought

Disorders of thought such as delusional ideas are common in SZ. Delusions of reference and persecution are the commonest, while delusional ideas of grandeur, religious content and bodily delusions are less common. Disorders of the train or the content of thought usually appear as loosening of associations. Other thought disorders include poverty of speech, thought rigidity and neologisms.

Perception

The commonest perceptual disorders are the hallucinations, especially the auditory ones. Visual, haptic, gustatory, olfactory and kinaesthetic hallucinations are less commonly observed.

Affect

Blunt, flat or inappropriate affect is common. It is difficult to be estimated accurately.

Sense of self

The sense of self in SZ is usually disturbed. There is loss of the boundaries of self which is manifested by confusion of identity and delusional ideas of external control.

Interpersonal functioning in relation to the external world

Almost always there is difficulty in interpersonal relationships. It is common for the patient to withdraw from the external world.

Psychomotor behavior

Apart from the intense stimulation which the patient exhibits in the acute phase (initial or relapse), a type of psychomotor disorder may occur later. It consists of resistance to commands

or movement attempts (catatonic negativism), catatonic stupor, catatonic excitement or taking inappropriate or paradoxical postures. Mannerisms, echopraxia or waxy flexibility occur.
The characteristic symptoms of SZ can be grouped into two categories: **positive symptoms**, resulting from growth or distortion of normal functions and **negative symptoms** resulting from a decrease or loss of normal functions.
Positive symptoms include disorders of thought content (delusions), perception (hallucinations), speech and communication [of the train of thought (disorganized speech, incoherence)] and of control of mobility (disorganized or catatonic behavior)]. Negative symptoms include disturbance of emotion (affective flattening or dullness), of speech and of goal-directed behavior.

Other symptoms and signs

There is often ritual or stereotypic behavior. Dysphoric mood is common and can take the form of depression, anxiety, anger, or a combination of these affects. Depersonalization and derealization are often seen. There is no disturbance of consciousness. However, in acute exacerbations, confusion, impaired orientation or even memory impairment may occur. Anhedonia, loss of libido and sleep disturbances may also occur. The schizophrenic patients often develop physical symptoms such as "soft" neurological signs (left/right confusion, impaired coordination of movements and automatic motor abnormalities).
Neuroimaging techniques (CT, MRI) have shown structural changes in the brain, such as enlargement of the ventricles and cerebellar atrophy. Decrease of the size of the basal ganglia and of the overall size of the brain has been observed. Functional brain imaging (SPECT, PET) have shown reduced blood flow or reduced glucose consumption in brain areas such as the prefrontal lobe. Neuropsychological tests show various dysfunctions, such as difficulty in focusing attention or difficulty in abstract thinking. Neurophysiological tests show slowing of reaction time (RT) and problems in eye tracking movements. None is pathognomonic.

Clinical picture and course

The onset of the disease is usually observed in early adult life. Strange behavior occurs, such as searching a private message to headlines or using words in a strange way. Slowly the person becomes withdrawn socially and loses his/her initiative and interests. At first, he/she may show

a significant degree of anxiety and hypersensitivity to external and interpersonal stimuli, but is slowly absorbed in his/her inner world. Blunt affect, poverty of speech, odd beliefs, preconceived ideas and ideas of reference occur. All these form the prodromal phase of SZ which can last for days or months.

Regardless of whether or not a prodromal phase occurs, all schizophrenics have what is called active phase, during which the psychosis is sharp and clear, and patients appear disturbed. In this phase, the characteristic psychotic symptoms dominate the clinical picture. The active phase can last for an indefinite time or just for a few weeks. Key to the diagnosis of SZ is the presence of psychotic symptoms in the active phase for at least 1 month. When the active phase subsides (with or without therapy), the patient usually does not return functionally to the previous premorbid level but enters a residual phase. Dullness or flattening of emotion and social withdrawal tend to be commoner in the residual phase. During the residual phase, some of psychotic symptoms such as delusions or hallucinations, may persist but are usually less emotionally charged. There is always the chance for complete remission, but the most common way is the occasional occurrence of acute exacerbations with increased residual damage in between episodes (American Diagnostic and Statistical Manual (DSM-IV), 2000, Kaplan & Saddock's, 2007, Gelder et al (2013).

Treatment

The treatment of SZ is a long process for the patient, the family and the health care team involved with the patient. The treatment of SZ comprises 1) physical treatments (antipsychotic drugs) and 2) psychosocial treatments (inpatient and outpatient). Treatment involves a long supply of biopsychosocial support system (Kaplan & Saddock's, 2007, Gelder et al, 2013).

General neurological findings in SZ

Structural changes in disease

Differences in the volume and structure of certain brain areas are seen between healthy and schizophrenics. However, no finding is diagnostic. This is due to the heterogeneity of the disorder. There is smaller volume of gray matter in certain areas. Brain ventricles size differences and differences in the volume of the hippocampus are also found. Most studies suggest that there is a decrease in the volume of the left medium temporal lobe and the left

superior temporal gyrus. It is not clear whether they are related to treatment with antipsychotic drugs. Defects in the ventricles and in the amygdala are due to the loss of glial cells than neurons per se (Gelder et al, 2013).

Functional disturbances in SZ

Neuropsychological tests together with imaging such as fMRI and PET examined brain activity and showed that differences occur in the frontal lobe, hippocampus and in the temporal lobes. PET findings indicate that the less the frontal lobes are activated in memory tests, the higher the dopamine activity is implicated in SZ (Kaplan & Saddock's, 2007, Gelder et al, 2013).

The retrospective study of Kandia and Yakoumaki (2012) showed that patients often exhibit disturbances in selective or prolonged attention, in learning, in verbal memory, in verbal fluency, in information processing speed, in psychomotor speed, in abstract capacity and in the general intelligence quotient (IQ). Correlation exists between the severity of negative symptoms and executive functions, visual-spatial memory and verbal working memory. The amelioration of the negative symptoms may lead to improvement in these fields of knowledge. Patients with SZ tend to have particularly large reduction on their cognitive functions of deductive ability, perceptual and psychomotor speed and vigilance in relation to controls and patients with bipolar disorder (Kandias & Yakoumaki, 2012).

Biochemical changes

Attention has been given to dopamine (DA) in the brain limbic system. This resulted from the finding that phenothiazines, which prevent DA function, reduce psychotic symptoms. Also amphetamines that cause release of DA exacerbate the psychotic symptoms of SZ. The DA hypothesis suggested that excessive activity of the D2 receptors was the cause of the positive symptoms of SZ. The hypothesis of DA is now considered simpler, since the newer antipsychotic drugs (atypical antipsychotics) are as effective as the older (typical antipsychotic). The neurotransmitter glutamate and the reduced activity of the NMDA receptor are of particular interest, since abnormal low levels of glutamate receptors were found in postmortem brains of schizophrenics. Also, the discovery that drugs which block glutamate such as phencyclidine and ketamine mimic the symptoms and cognitive disturbances associated with the disease has also increased the interest in the glutamate hypothesis in SZ (Berry et al, 2003).

CHAPTER ONE

Brain networks and pathways-normal sensorimotor functioning-Reference to SZ

I.Frontal lobe

Frontal-subcortical neuronal circuits

The frontal-subcortical circuits form the principal network, which mediates motor activity and behavior in humans. Five parallel frontal-subcortical circuits link specific areas of the frontal cortex to the striatum, basal ganglia and thalamus (Alexander et al, 1986). These frontal–subcortical circuits originate from the supplementary motor area, frontal eye field, dorsolateral prefrontal region, lateral orbitofrontal region and anterior cingulate of the frontal cortex. Afferent and efferent connections to the frontal-subcortical circuits mediate coordination between functionally similar areas of the brain.

The five defined frontal-subcortical circuits are named according to their function or site of origin in the cortex. The motor circuit originating in the supplementary motor area and the oculomotor circuit originating in the frontal eye fields are involved in motor functions. The dorsolateral prefrontal, orbital frontal and anterior cingulate circuits are involved to executive functions, social behavior and motivational states in humans. Depression, obsessive-compulsive disorder (OCD), SZ and substance abuse all involve the frontal-subcortical circuits.

Anatomy of frontal–subcortical circuits

The main anatomical structures are the same for all circuits. They originate in the prefrontal cortex, project to the striatum (caudate, putamen, ventral striatum), connect to the globus pallidus and substantia nigra and from there they connect to the thalamus. There is a final link back to the frontal cortex and each circuit forms a closed loop. They have though “open loop” connections (fig.1.1).

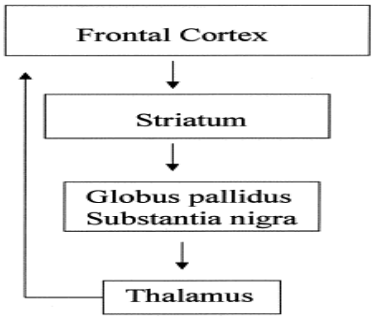


Fig. 1.1. General structure of frontal subcortical circuits (Tekin & Cummings, 2002)

The structures of the circuits remain segregated as they pass through the caudate and putamen, globus pallidus, substantia nigra and thalamus. The dorsolateral frontal cortex projects to the dorsolateral part of the caudate nucleus, the orbitofrontal part projects to the ventral striatal areas and the anterior cingulate cortex projects to the medial striatal and nucleus accumbens region (Mega & Cummings, 1994). The projections from each level are progressively connected to smaller areas as they proceed from cortex to subcortical structures. Each circuit is also preserved as a discrete anatomical structure (Cummings, 1995).

There are two pathways within each circuit: a direct pathway connecting the striatum and the globus pallidus interna-substantia nigra complex, and an indirect pathway linking striatum to globus pallidus externa, then to subthalamic nucleus and back to globus pallidus interna-substantia nigra (Alexander et al, 1990). Both direct and indirect circuits modulate input to the thalamus. Dysfunction in the direct circuit causes abnormal thalamic inhibition, whereas indirect circuit dysfunction leads to disinhibition and thalamic overactivity. Each set of the circuits is present in each hemisphere.

The *motor circuit* originates from neurons in the supplementary motor area, premotor cortex, motor cortex and somatosensory cortex. These areas project topographically to the putamen. The putamen in turn projects to specific parts of the globus pallidus externa, interna and substantia nigra pars reticularis. The globus pallidus connects to the ventrolateral, ventral anterior and central median nuclei of the thalamus which project back to the motor cortex (Mega & Cummings, 1994).

The *oculomotor circuit* originates in the frontal eye field (Brodmann's area (BA) 8) and posterior parietal cortex. The fibers then project to the body of the caudate nucleus, dorsomedial globus pallidus and ventrolateral substantia nigra. They reach the mediodorsal thalamic nuclei and close the loop by projecting back to the frontal eye field.

The *dorsolateral prefrontal circuit* originates in BA 9 and 10 on the lateral surface of the anterior frontal lobe and projects to the dorsolateral head of the caudate nucleus. Neurons from this site project to the lateral part of the mediodorsal globus pallidus interna and rostrolateral substantia nigra as the direct pathway. The fibers from the basal ganglia project to

parvocellular portions of the ventral anterior and mediodorsal thalamus. The mediodorsal thalamus sends fibers back to the circuit's start in the dorsolateral frontal cortex (fig. 1.2).

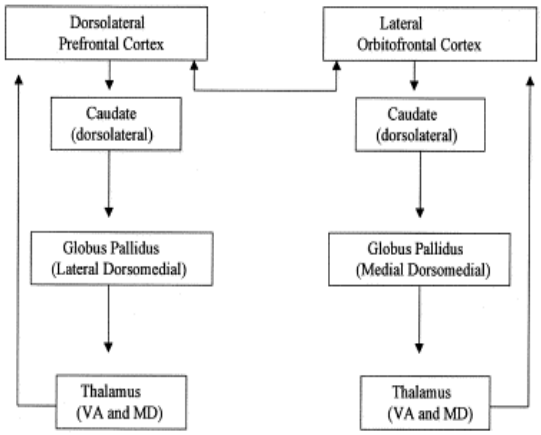


Fig. 1.2. Anatomy (direct pathways) of dorsolateral prefrontal and lateral orbitofrontal subcortical circuits VA=ventral anterior; MD=mediodorsal (Tekin & Cummings, 2002)

The *lateral orbitofrontal circuit* originates in BA 10 and 11 and sends fibers to the ventromedial caudate nucleus. Neurons form this region of the caudate project to the medial part of the mediodorsal globus pallidus interna and to the rostromedial substantia nigra. Fibers from substantia nigra and globus pallidus connect to the ventral anterior and mediodorsal thalamus. The circuit is closed by fibers projecting back to the orbitofrontal cortex from thalamus (fig. 1.2).

A *medial division of the orbitofrontal circuit* has also been described. It originates in the gyrus rectus and the medial orbital gyrus of BA 11 (Mega et al, 1997). The projections go to the medial parts of the accumbens, to the medial ventral pallidum and reach the mediodorsal thalamic nucleus (fig.1.3).

The *anterior cingulate circuit* originates in the anterior cingulate cortex (BA 24). The neurons project to ventral striatum, which includes the ventromedial caudate, ventral putamen, nucleus accumbens and olfactory tubercle. This area is the "limbic striatum." Projections from the ventral striatum pass to the rostromedial globus pallidus interna, ventral pallidum and rostrodorsal substantia nigra. The ventral pallidum connects to the ventral anterior nucleus of the thalamus. The anterior cingulate circuit is closed with projections from the ventral anterior thalamus back to the anterior cingulate cortex. The limbic system connections involve both the anterior cingulate and the medial frontal regions (Fig.1.3).

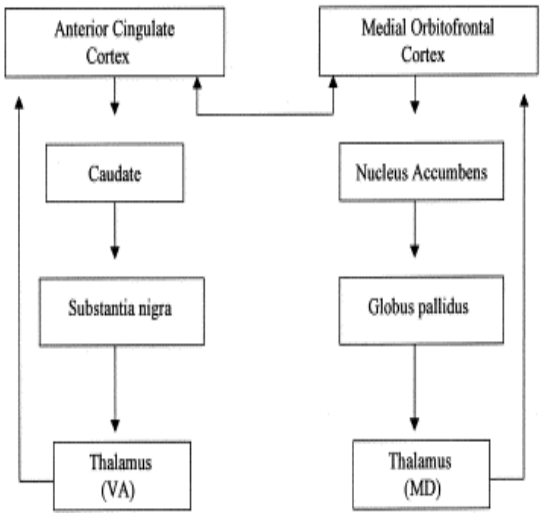


Fig. 1.3. Anatomy (direct pathways) of medial orbitofrontal and anterior cingulate circuits VA=ventral anterior; MD=mediodorsal (Tekin & Cummings, 2002)

Neurochemistry of frontal–subcortical circuits

Neurochemical structure

The fibers in each circuit originating from the frontal lobe are mediated by excitatory glutaminergic neurotransmission. They project to the striatum, which is formed by the caudate, putamen and ventral striatum. The connections from the striatum to the globus pallidus interna–substantia nigra complex as the direct pathway, and to the globus pallidus externa as the indirect pathway, are both inhibitory and are mediated by γ-aminobutyric acid (GABA). In the indirect pathway (globus pallidus externa) project inhibitory GABA fibers to the subthalamic nucleus which then connects to the globus pallidus interna–substantia nigra complex via excitatory glutaminergic fibers. The globus pallidus interna–substantia nigra complex then projects to thalamus through inhibitory GABA fibers. The final connections from the thalamus to the frontal lobe are glutaminergic and excitatory (Bronstein & Cummings, 2001). In the frontal–subcortical circuits, the corticostriatal information processing is modulated by different neurotransmitter systems.

Dopaminergic neurons from the substantia nigra project to the striatum and affect all frontal–subcortical functions. The inhibitory and excitatory effects of DA are dependent on the type of receptors with which it interacts postsynaptically. Five different (D1–D5) DA receptors are defined. The substantia nigra has inhibitory connections with the indirect pathways of the

frontal–subcortical circuits via D1 receptors and excitatory connections with the direct circuits via D2 receptors. There are nigral connections with the limbic circuits, rich in D3 and D4 receptor subtypes. This allows the interaction between the emotional input and motor activity, cognition and motivation. This anatomical structure shows the DA effects on motor activity, motivation, thought and behavior (Mega & Cummings, 1994).

The cholinergic interneurons are located in the striatum and modulate the thalamic activation of the cortex. The pedunculopontine and lateral tegmentum are the principal areas, which send cholinergic input to the thalamus. The cortical areas receive their cholinergic input mainly from the nucleus basalis of Meynert (Parent et al, 1988, Mesulan, 2000). There are interactions between the cholinergic and dopaminergic systems. D2 DA receptors, located in cholinergic interneurons, inhibit acetylcholine release, whereas D1 receptor agonists enhance acetylcholine release (McGeer & McGeer, 1993).

Serotonin receptors (5HTs) are distributed at different levels of the frontal–subcortical circuits. The 5-HT1 receptor is the most abundant in the basal ganglia. 5-HT3 receptors are located mostly in the ventral striatum, hippocampus, septal area and amygdala contributing to the modulation of mesocortical and mesolimbic dopaminergic pathways. Interactions between dopaminergic and serotonergic systems may provide a basis for effects of serotonergic antagonists in diseases with excess DA, like SZ.

Glutamate acts primarily through effects on NMDA receptors. Corticostriatal and thalamo-cortical projections are glutamatergic. Glutamate stimulates striatal DA release. NMDA receptor blockade decreases basal cholinergic release. The interactions between glutamate, DA and acetylcholine serve as a corticostriatal–thalamocortical negative feedback loop to limit cortical overstimulation.

GABA is the predominant neurotransmitter in the basal ganglia. The direct pathway consists of inhibitory GABA striatal fibers extending to the internal segment of globus pallidum and substantia nigra.

Cortical stimulation of the striatum inhibits the globus pallidus and reduces the effect of inhibitory GABAergic projections to the thalamus. This reduces the thalamic inhibition and enhances the thalamocortical excitation.

Dorsolateral prefrontal syndrome

The dorsolateral prefrontal circuit is involved mainly in executive function. It includes abilities to solve complex functions like learning new information, planning ahead, activating remote memories, regulating actions according to the environmental stimuli, shifting behavioral sets appropriately, generating motor programs and temporal ordering of recent events (Duffy & Campbell, 1994). Patients with dorsolateral prefrontal circuit dysfunction are usually perseverative and show impaired reasoning with dysfunction in mental flexibility. They show inability to maintain and redirect their attention. They are easily distracted during neuropsychological testing. Without constant direction from the examiner, they may exhibit disorganized behavior. They show decreased performance in the Wisconsin Card Sorting Test (WCST), which requires strategy generation and organization of behavior. Verbal and design fluency and Luria's tests are poor (Duffy & Campbell, 1994).

Orbitofrontal syndrome

The orbitofrontal circuit connects the frontal monitoring systems to the limbic system. Dysfunction of the circuit is characterized by personality change including behavioral disinhibition and emotional lability. The patients respond inappropriately to social clues and lack interpersonal sensitivity, empathy and judgement (Miller et al, 1993).

Anterior cingulate syndrome

The anterior cingulate mediates motivated behavior. Lesions in this area are associated with decreased motivation. Akinetic mutism occurs with bilateral lesions of the anterior cingulate.

Frontal–subcortical circuits and neuropsychiatric disorders

A variety of neuropsychiatric disorders have associations with frontal-subcortical circuit dysfunction, especially schizophrenia (SZ). SZ has been associated with frontal lobe dysfunction as well as abnormal regulation of subcortical DA systems (Goldman-Rakic & Seleman, 1997). Functional imaging studies in patients with SZ, show decreased cerebral blood flow in the dorsolateral prefrontal cortex during a variety of cognitive tasks (Andreasen et al, 1994). Frontal lobe glucose utilization also is decreased in SZ patients with prominent negative symptoms ((Tamminga et al, 1992). Postmortem and structural imaging studies reveal a reduction in the cortical volume in patients with SZ (Breier et al, 1992).

The cortex regulates subcortical dopaminergic function. It has been suggested that "hypofrontality" in SZ may lead to hyperactivity of subcortical dopaminergic systems. Lesions in the prefrontal cortex enhance the responsiveness of subcortical dopaminergic system to pharmacological challenge. Augmentation of dopaminergic transmission in the frontal cortex, suppresses subcortical DA turnover and release (Roberts et al, 1994, King et al, 1997).
The nucleus accumbens, which receives excitatory input from multiple frontal cortex and limbic structures, also is thought to be dysfunctional in patients with SZ. The nucleus accumbens is involved in both the glutamatergic and dopaminergic neurotransmission. Deficits of sensory filtering in schizophrenics suggest involvement of the ventral pallidum and thalamus in the disease.

Assessing psychomotor function

Psychomotor activities may be either discrete or continuous. They may consist of a single movement or of a sequence of movements. All are cognitive activities, sometimes acquired after many months or years of practice. They express our capabilities. They are also essential in our daily care activities.
Higher order executive control is involved in the planning of the movement sequence, task switching, inhibition of inadequate responses, performance monitoring, and error detection. All the above parameters affect psychomotor speed. They are frequently disturbed in SZ (table 1.1).

Table 1.1 The neurocognitive processes that support motor control

Process	Function in motor control	Anatomic locus
	Goal or action selection Switching to more optimal actions	
Strategic	Inhibition of unwanted tendencies	Various regions in frontal cortex
Perceptual motor integration	Selection of spatial targets Transfer to egocentric space	Parietal cortex Premotor cortex
Sequencing	Ordering of movements in the correct sequence	Basal ganglia and supplementary motor cortex
Timing and force control	Adjustment of time and force of movements or muscle commands	Cerebellum
Dynamic	Innervating muscles	Motor cortex
Monitoring	Evaluating outcome	Medial frontal cortex

Modified from Willingham (Morrens et al, 2007)

Assessing psychomotor speed

Fine motor tests

A group of tests examines motor actions without needing higher order cognitive processes. It includes tasks that require the maintenance of maximal speed over brief periods of time (finger tapping, pronation-supination test) or rapid fingertip manipulations (pin test, pegboard tasks). Tasks which examine fine and repetitive movements test functions such as motor coordination and visuospatial monitoring.

Drawing and writing tasks

Handwriting is slowed in schizophrenic patients. To investigate slowing of fine motor movements in patients, some researchers used tablets to record performance on drawing and writing tasks. Subjects draw or copy the presented stimuli on a digitizer that is connected to a PC so that reaction time (RT) is measured and various stages of the movements are assessed Movement control is the result of strategic and perceptual motor integration, sequencing, and muscular dynamic processes. Thus, even the simplest movement depends on the activation of several different processes. Schizophrenics are slowed, even when they copy a simple line (Morrens et al, 2007).

Gross motor tasks

Ultrasonic movement analysis found decreased gait velocity in neuroleptic-naive schizophrenics. This resulted from reduced stride length rather than from step frequency. These gait disturbances worsened after conventional but not atypical antipsychotic treatment (Morrens et al, 2007).

Tasks sensitive to speed of information processing

Classical processing-speed tasks

Tests assessing speed of information processing are widely used in cognitive studies of SZ. Typical examples are the Symbol-digit substitution test (SDST), the Trait making test (TMT), or the Stroop color-word test (Morrens et al, 2007). These tests are all sensitive to psychomotor slowing (PS) although they primarily investigate a wide range of cognitive functions, known to be affected in schizophrenics, such as working memory (WM) or attention. Thus, they are not the most appropriate tools for the assessment of speed of psychomotor functioning.

Reaction-time (RT)

RT has systematically been shown to be impaired in schizophrenics. RT trials involve the rapid initiation of responses, elicited by external cues. Although they have a psychomotor component, RTs are mainly sensitive to deficits in vigilance and processing speed (Morrens et al, 2007).

II. Parietal lobe

The parietal cortex (PC) integrates information from different sensory sources. Tracts from two or more sensory systems are integrated by the posterior parietal cortex (PPC). This area is responsible for perceptions, such as space dimension and action guiding. The parietal lobe includes the PPC as well as the dorsal stream of the visual system. This region maps objects perceived visually into body position coordinates. Experiments in primates established a link between parietal areas and types of cognitive motor control. The intra-parietal sulcus has been associated with saccadic eye movement and attention. The intra-occipital parietal junction and the medial-occipital parietal junction are related to movement execution. Therefore, the parietal cortex participates in several aspects of motor action, from early object identification and selection for action, until the final stage of executing it precisely (Teixeira et al, 2014, fig 1.4, fig.1.5).

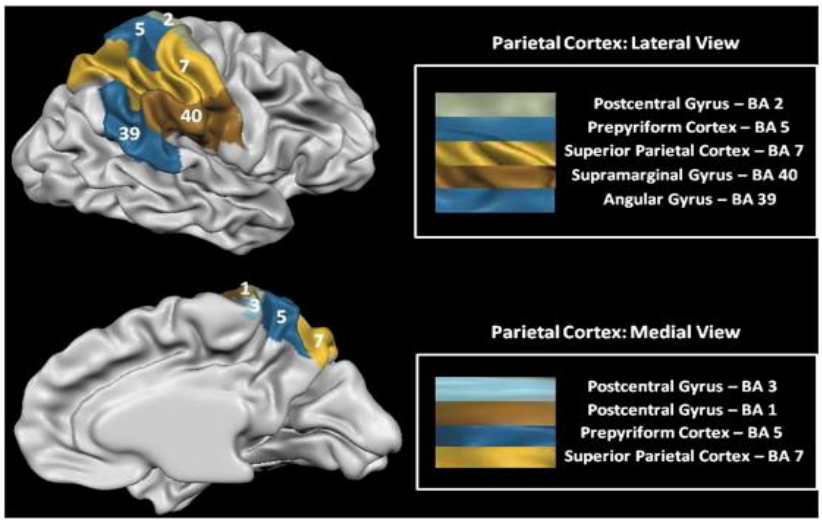


Fig.1.4.The parietal cortex is fundamental for sensorimotor integration processes. Its sub-areas are responsible for different functions in sensory processing, memory, attention and movement anticipation. It is located behind the frontal lobe and above the occipital lobe. The primary and secondary somatosensory cortices SI and SII (BA 1, 2, 3 and 5) are found immediately behind the central sulcus, and between this and the posterior parietal cortex. The primary somatosensory cortex (SI), located in the postcentral gyrus, is the main sensory receptive area for the sense of touch, known as the sensory homunculus (Teixeira et al, 2014)

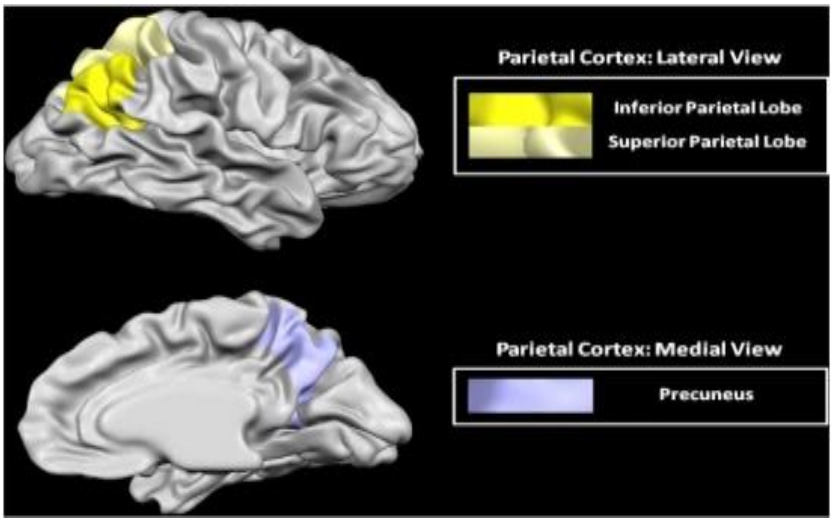


Fig. 1.5. PPC is divided into lateral and medial segments, where the latter include mainly the precuneus. This structure is directly involved in face perception. The lateral parietal cortex has direct connections with the dorsal lateral prefrontal cortex, temporal cortex and medial parietal regions, as well as reciprocal connections with the hippocampus, parahippocampus and medial regions of the temporal lobe. The parietofrontal connections mediate the transformation of visual information into action. Reaching, grasping and eye movements are guided by the caudal SPL and the intra-parietal sulcus linked to the frontal cortex and frontal eye fields (Teixeira et al, 2014)

Sensory motor integration processes

The brain integrates visual, proprioceptive and sensory inputs into spatial and sensorimotor representations of the environment and produces appropriate motor responses. This process does not occur in specific areas, but rather through integration of sensory modalities. The parietal cortex has been associated with spatial perception, spatial attention, representation and retention of sensory information. Spatially, motor behavior requires the nervous system to extract the sensory information from the positions of the body, and, at the same time, distinguish the peripheral sensory feedback from the environment. The PPC is actively involved in the planning of reaching movements, visual-motor integration and decision-making for motor actions. Thus, the parietal cortex supervises so that the movements are well executed (Teixeira et al, 2014).

Hand movement control: reaching, grasping and pointing

The sensory organs (vision and proprioceptive receptors) obtain information about objects. Thus, through the sensorimotor integration process, sensory information is transformed into motor data. This process promotes our ability to adapt motor actions or create new ones

according to environmental demands. PPC plays a major role in the performance of these movements (fig.1.5).

Different parietal areas also play a specific role during visuo-motor coordination. The left superior parietal lobule activation is a spatial shifting mechanism to direct us to the selected stimulus. Increased left parieto-occipital activity has been associated with higher demands of selection and motor planning. The right intra-parietal area plays a role in the identification of the object during less automatic tasks.

Functional MRI studies demonstrated activation of the precuneus, the medial, anterior intra-parietal and superior parietal cortex during both visual and non-visual reaching. Humans have multiple parietal regions and cortical networks for reaching which activate for each sensory condition (Teixeira et al, 2014).

Saccadic eye movement (SEM)

The parietal cortex is widely studied for its involvement in the control of saccadic eye movements (SEM), especially on the onset of the movement. It is connected with other regions that contribute to saccades' control, such as superior colliculus and frontal eye field. Furthermore, it has an important role in visuospatial attention processing, first because of its involvement in mental representation of visual stimuli, and second due to its participation in the transforming of sensorial stimuli into motor command. Studies showed that individuals with PPC lesions present an increase in saccade latency and errors in target precision. Studies of patients with parieto-occipital junction lesions suggest involvement of this area in a set of visuo-perceptual skills, such as the visual identification of objects in visual search and direction of the eye toward the target. This region also is involved in sensory integration, especially eye-hand coordination (Teixeira et al, 2014).

Movement observation: parietal areas and sensory-motor transformations

The ability to generate internal representations of motor actions is part of the cortical motor function. Individual motivation combined with external factors determines whether these representations will be converted into real actions. Complex sensory-motor transformations occur within the parietal cortex and motor areas. The transformation of an observed action into a real one is important. The motor areas have a matching mechanism where observed activities

relate to an internal representation of that motor action (mirror mechanism). Therefore, motor areas are involved in decision-making processes leading to the initiation of an effective motor act (Teixeira et al, 2014).

The example of optic ataxia disorder (OA)

The OA disorder provides information for the way visual information is used by the perceptual motor system to control action. Patients who have this disorder fail to identify peripheral visual targets, but are able to reach targets through proprioceptive and auditory information. OA causes no damage to the motor system and does not impair spatial localization. The observed visuo-motor deficits have been related to failure in transforming the visual information to produce a coordinate action. Lesions of the PPC, specifically of the dorsal stream, the superior parietal lobule and the parieto-occipital junction of the intra-parietal sulcus, are responsible for OA (Teixeira et al, 2014). The involvement of these brain areas alters the representation of the visual space contralateral to the damaged hemisphere, and the movement of the contralesional hand becomes more impaired as the target becomes more eccentric. The parieto-occipital junction is activated during the identification of targets in the peripheral visual field, and is responsible for updating control along with the intra-parietal sulcus. The superior parietal lobe controls visually guided reaching tasks and is responsible for tactile object recognition. The patient with OA is able to describe the direction of an object, but cannot match the hand movement to reach the object. There is damage in the PPC dorsal stream, which is a crucial structure for the maintenance of visual awareness and for the identification of the object spatial properties. OA is due to a disconnection between the visual input and the output of motor commands (Teixeira et al, 2014).

III. Parietal lobe in SZ

The parietal cortex (especially the inferior parietal lobule (IPL)) received little attention compared to the prefrontal cortex, hippocampus, or cingulate. It is a difficult region to study (Maruff et al, 2005).

One reason is histological complexity. The IPL consists of the supramarginal gyrus (BA 40) and adjacent angular gyrus (BA 39). Histological studies of the IPL showed that it is divided into 7 cyto-architectonic areas, 5 in BA 40 and 2 in BA 39 (Zilles et al, 2003, Caspers et al, 2006).

Studying random sections from either BA may yield peculiar findings. A second reason is that the IPL is one of the last areas of the human brain to mature. Flechsig identified the supramarginal and angular gyri as among the last areas to myelinate (Flechsig, 1920). Geschwind (1965) said that the IPL was “one of the last cortical areas in which dendrites appear” and that “it matures cytoarchitechtonically very late, often in late childhood.” Due to its late development, the IPL is anatomically highly variable. Finally, studying the IPL is difficult because it is one of the most lateralized areas of the brain and very close to the planum temporale, which in the dominant lobe includes Wernicke's language area.

The relative importance of the two hemispheres in SZ remains controversial (Nasrallah, 1986), although there is evidence for decreased cerebral lateralization in this disease (Dollfus et al, 2006). In addition to being lateralized, the IPL shows sexual dimorphism. The left IPL is larger in males than in females. This implies cognitive differences between sexes (Frederikse et al, 1999).

Among the first reports of IPL structural abnormalities in individuals with SZ was that by von Angyal (1934), who noted that “from histological studies, it appears that the IPL belongs to the cortical regions most seriously damaged by SZ.” Von Angyal based his opinion on the neuropathological studies of Miskolczy. After studying the brains of 13 schizophrenics, Miskolczy concluded that neuronal cell losses and mild glial proliferation were more evident in the prefrontal, superior temporal, temporal pole, and IPL (Miskolczy, 1933). Currently all structural studies of the IPL are done with neuroimaging (table 1.2).

Thus, according to the literature, the parietal lobe integrates information from the visual, auditory and tactile sensory modalities, in order to evaluate it and plan a response.

The disruption of sensory integration is one of the earliest and most common symptoms of SZ. According to one study, “perceptual dysfunction is the most invariant feature of the early stages of SZ” and is found in almost two-thirds of patients (Cutting & Dunne, 1989).

Since under normal conditions, the IPL integrates the multiple sensory data as they arrive, when it is not functioning, the individual may be flooded with stimuli. The person cannot integrate sensory data into a coherent pattern. With such difficulty, schizophrenics may respond inappropriately. This may also lead to thought blocking. It may also produce loosening

of associations. Most aspects of thought disorder are probably explainable as defects in the sensory integration system of the IPL and other parts of the parietal cortex.

Table 1.2 Imaging studies of inferior parietal lobule in SZ (Teixeira et al, 2014, references in Teixeira et al, 2014)

Authors and year	Number of subjects with schizophrenia	Significant results
Goldstein et al. (1999)	29	↓ R and L supramarginal gyrus
Niznikiewicz et al. (2000)	15 (males only)	↑ R angular gyrus and reversed IPL asymmetry
Frederikse et al. (2000)	15	↓ L IPL volume in males and reversed IPL asymmetry in males
Wilke et al. (2001)	48	↓ IPL volume correlated with severity of symptoms
Hulshoff et al. (2001)	159	↓ R supramarginal gyrus
Kubicki et al. (2002)	16 (first episode)	↓ R IPL
Shapleske et al. (2002)	72	↑ R supramarginal gyrus
Buchanan et al. (2004)	44	↑ R supramarginal gyrus and reversed IPL asymmetry
Nierenberg et al. (2005)	14 (first episode)	↓ L angular gyrus
Zhou et al. (2007)	53	↓ R and L supramarginal gyrus
		↓ R and L angular gyrus and reversed supramarginal asymmetry

Additional examples of impaired sensory integration are neurological soft signs (NSS) such as astereognosia, graphesthesia, and double-simultaneous stimulation. Studies have shown that at least half of individuals with chronic SZ have such abnormalities (Torrey, 1980, Manschreck & Ames, 1984). They also occur in individuals who have never been treated with antipsychotic medication (Keshavan et al, 2003).

NSS have been linked to dysfunction of the parietal lobes especially to the supramarginal gyrus (Critchley, 1953, Lishman, 1978). Critchley also noted the important role of the parietal lobes in forming “corporal awareness” (Critchley, 1953). The role of the posterior parietal in corporeal awareness has been confirmed through the years (Berlucchi & Aglioti, 1997). Disturbances in body image have been extensively described in individuals with SZ. Cutting (1989) reported disorders of body image in 45% of SZ admissions. The commonest manifestations were alterations in structure, shape, or weight. A very common disturbance of body image in

schizophrenics is right–left disorientation. The most serious disturbance of body image associated with parietal lobe damage is neglect of one side of the body.

Individuals with SZ often experience disruptions in their sense of self, especially in the early stages of their illness (Sedman, 1970). Usually it is depersonalization or derealization. One dramatic disruption of the sense of self is the feeling that one's thoughts or actions are being influenced or replaced by those of an external agent (Spence et al, 1997). They are referred to as delusions of passivity. Schneider listed them among the “first rank” symptoms of SZ (Schneider, 1959).

Several studies have linked delusions of passivity in SZ to the IPL. An fMRI study where normal controls were led to believe that another person was controlling their actions reported associated activation of the IPL (Farrer & Frith, 2002). In an MRI structural study, schizophrenics who had passivity delusions were compared to those who did not. The former group had significant reductions in gray matter volume in the right supramarginal gyrus and the left prefrontal region (Maruff et al, 2005). A PET scan study compared 7 individuals with SZ with passivity delusions, 6 without such delusions, and 6 normal controls. Passivity delusions were associated with hyperactivation of the right supramarginal gyrus and cingulate gyrus (Spence et al, 1997). Such studies showed passivity phenomena to be associated with hyperactivity *i*n the parietal cortex, lateralized to the right hemisphere (Dankert et al, 2004).

Sustained attention is known to be impaired in many individuals with SZ. Mesulam & Geschwind (1978) noted that “a lesion in the IPL may result in disconnection of the cortex from the limbic system” and produce attention deficits. An MRI study of neuroleptic-naïve individuals with SZ using the Continuous Performance Test (CPT) as a measure of sustained attention reported significant correlations between CPT performance and gray matter volume in the left supramarginal and angular gyri (Salgado-Pineda et al, 2003). The authors concluded that these regions are involved in the attentional impairment of SZ.

Working memory (WM), also known to be impaired in SZ, involves the IPL. Using fMRI, Kindermann et al (2004) reported diminished WM response in SZ patients in the left supramarginal gyrus (BA 40) as well as in other regions. Jansma et al (2004) also carried out an fMRI study of WM in SZ and found that the supramarginal gyrus was bilaterally involved.

There are additional executive functions known to involve the IPL. Dual-task management, which many schizophrenics find difficult, has been shown to involve the supramarginal gyrus as well as the prefrontal cortex (Collette et al, 2005). And in an fMRI study of decision-making in individuals with SZ, the supramarginal gyrus was activated significantly more in the patients than in the controls (Paulus et al, 2002). These results support the hypothesis of a prefrontal-parietal cortex dysfunction during decision-making in SZ patients. A PET study of schizophrenics with “psychomotor poverty syndrome” (decreased speech, movement, and expression of affect) found decreased blood flow in the supramarginal and angular gyri (Liddle et al, 1992). Thus, the symptomatology may be determined by the relative degree of pathology in the prefrontal-temporal-inferior parietal axis.

CHAPTER TWO - Decision making (DM) in health-reference to SZ

The rational decision making (DM) involves three steps: (1) identification of all alternatives, (2) determination of the consequences of each alternative, and (3) comparison of the accuracy and efficiency of each consequence (Simon, 1959). DM is a constant process in life. Many theories have tried to explain the way DM is taking place.

Drive theory claims that organisms have needs. The primary needs are related to survival (food and shelter). The secondary needs are related to the organism's well-being and comfort. For satisfaction of these needs organisms are driven to action. This is motivation. When a need is satisfied, the drive is reduced and the person returns to a state of homeostasis.

Skinnerian models deny the existence of inner non-observable phenomena, including motivation. Skinner defined DM as a process in which behavior is solely determined by its consequences. Organisms learn through experience to behave in order to obtain rewards and avoid punishment. Thus, DM is related to previous experiences and their consequences.

In an environment where the consequences of choices are certain and constant, the option with the highest value would be the preferred one. However, this situation is rarely encountered. Expected value alone is often a poor predictor of choice. Risk is present when multiple possible outcomes can occur.

Kahneman and Tversk developed prospect theory, which explains how humans calculate value nonlinearly. This theory is supported by findings of nonlinear striatum activity. It explains phenomena such as larger aversive response to losses compared with favorable response to comparable gains, and a strong preference for certainty (Caceda et al, 2014).

Game theory attempts to predict the strategies with which a group of decisions will be made as people try to maximize their profits. It relies on two basic assumptions: first, individuals only seek to maximize their own profit, and second, in order to achieve this they behave rationally. Nash equilibrium refers to a set of strategies from which no individual player can increase his payoff unilaterally. However, results from experiments in both human and nonhuman primates have proved the Nash equation non-applicable.

In social contexts, DM is not purely driven by self-interest, but also by considerations about the well-being of other individuals. To better characterize DM in social contexts, socially oriented emotions such as fairness and altruism should be considered.

Cognitive processes of decision-making (DM)

Cognitive control refers to the ability to direct behavior flexibly and in accordance with a variety of goals. The functions of cognitive control include error detection and correction mechanisms, conflict resolution, response inhibition, task-switching, and emotion regulation. Although cognitive control was initially considered to be a frontal cortex function, research has identified a "cognitive control network" that includes the dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), parietal cortex, motor areas, and cerebellum (D'Esposito, 2007).

In general, DM is a process in which the individual tries to increase the potential of benefits through the selection of responses that lead to positive results in given circumstances. This process plays a major role in everyday choices, establishing priorities and avoiding alternatives which may be harming.

In neurobiological terms, the processes that represent the complex decisive mechanism involve distinct brain areas, whose common objective is filtrating information, selecting several stimuli and expressing an appropriate behavior adjusted to the external environment.

The association between lesions in specific brain areas, changes in social behavior and DM was initially established by Harlow (1848), when describing the "Phineas Gage case." However, only after the 1990's the interest in the research of emotional changes as a result of neurological lesions was established, through the studies by Damasio et al (1990, 1996). Using the dermal conductance response (DCR), Damasio assessed patients with lesions in the orbitofrontal prefrontal cortex (OFPC). Although there was preservation in the global intellective functioning, the OFPC group revealed inability in applying the knowledge they had in contexts which reproduced situations of choice. For Damasio, this inability was attributed to failure to use "somatic markers" (positive or negative valences as measured by DCR).

One of Damasio's collaborators, Bechara (2005) developed neuropsychological tests sensitive to OFPC assessment, creating the Iowa Gambling Task (IGT), a game of cards known as "gambling

test". This simulates DM situations based on the choice of cards considered as high or low risk. Patients made persistent disadvantageous choices, even in situations in which they were previously warned about the possible unfavorable consequences of their decisions. Such behavior became known as "insensitivity to future consequences" or "myopia for the future." Other techniques which have been used to investigate neural connections underlying DM are PET and MRI. These imaging techniques provided evidence for the involvement of orbital prefrontal regions (orbitofrontal and orbitomedial) in processes of choice, reward and punishment. They backed up the IGT findings for DM.

PET and fMRI studies showed activation of different OFPC areas, with tasks assessing DM processing. Methodologically similar studies investigated reward processing and also found activation of orbitofrontal areas. The last 10 years research on DM mechanisms and their relation with cortical areas has been applied to the investigation of psychiatric disorders. Paulus (2007) studied interactive affective and cognitive processes involved in healthy DM. He found that if a homeostatic balance was not reached by an individual during interactive affective and cognitive processes, poor decisions might result. He also reviewed neural network and functional brain imaging studies conducted while DM tasks were being performed by a variety of subjects' samples. Paulus (2007) reported that the general DM processes are complex and dynamic homeostatic systems regulated by several areas of the brain. Optimal outcomes of decisions are dependent on the interplay of peripheral, central, sensory and cognitive processes. He also stated that neuroimaging studies identified interactions of cortical and subcortical portions of the limbic system which create a balance and produce exploratory action plans of the decision-maker. These decisional strategies also rely on relative value assessments. Thus, he concluded that non-optimal decisions would be made if homeostatic balance was not reached as a result of dynamic affective and cognitive processes.

Other researchers used a computational learning model to capture how people attended to goal-actions. Using representational simulation analyses of fMRI data, they demonstrated that neural representations in left anterior hippocampal cortex (HPC) corresponded with model predictions of concept organization (Mack et al, 2016). They showed that during early learning, when concept updating was most important, HPC was functionally coupled with prefrontal

regions. They proposed that when task goals change, object representations in HPC are organized in new ways, resulting in updated concepts that highlight the most critical features of the new goal (Mack et al, 2016). The prefrontal cortex (PFC) tunes selective attention to relevant features and compares that information with the existing conceptual knowledge in the HPC, updating the organization of items based on the new relevant features.

Fig.2.1 During learning, the hippocampus (HPC) (orange), in concert with prefrontal cortex (PFC) (blue), builds conceptual knowledge for a given goal. When goals change, new learning in HPC and PFC updates knowledge (Mack et al, 2016)

Neurochemistry and DM

When presented with an unexpected pleasurable stimulus or reward, dopaminergic neurons increase their firing. These brain responses are subsequently evoked by a conditioned stimulus after pairings with the reward. Further, the activation of DA neurons decreased with extinction trials when the expected reward is omitted. Research shows that these neurons actually fire in anticipation of future rewards. Thus, dopaminergic neurons seem to encode the likelihood of a rewarding outcome and generate a continuous update of its prediction accuracy. DA is therefore believed to provide a teaching signal to parts of the brain responsible for acquiring new behaviors. Serotonin closely interacts with DA along two different axes: reward (DA)-punishment (serotonin) and behavioral activation (DA)-inhibition (serotonin). The role of serotonin seems to counteract impulsivity, possibly by enhancing aversion and increasing behavioral inhibition. Although DA promotes behavioral activation to seek rewards, serotonin serves to inhibit actions where punishment may occur (Caceda et al, 2014). Data also support that the cognitive processing of uncertainty is related to the dorsomedial prefrontal cortex (DMPFC), whereas the affective reaction is associated with the OFC and insula (Caceda et al, 2014).

Cognitive processes of DM in schizophrenia (SZ)

Individuals with SZ have abnormalities in the prefrontal and emotional regulatory systems of the brain (Heerey et al, 2008). These dysfunctions are known to result in faulty cognitions and negative judgments. Deficits in WM and cognitive errors result in an underestimation of the impact of losses and vulnerability to harm. These may be the most influential factors that impair general DM among individuals with SZ (Heerey et al, 2008). Learning and complex DM are linked to prior experiences in order to produce new information (Newell & Bröder, 2008). Evans et al (2005) conducted a study of schizophrenics where cognitive processes involved in DM were examined in the context of performance on gambling tasks. For individuals with SZ, subjective experience was a more powerful predictor than behavioral scores. Their decisions were more likely based on emotion versus logic.

Greig et al (2007) conducted a year-long randomized controlled trial using a cognitive program based on learning, attention, language, executive function, and memory tasks. In the sample there were 72 individuals with SZ or schizoaffective disorder. They found that frequent, systematic reinforcements and reminders of acquired skills are important in cognitive function. Optimistic bias was investigated among individuals with SZ and non-ill subjects, regarding how this may influence DM (Prentice et al, 2005). They found that both groups had optimistic biases but non-ill subjects demonstrated a greater degree of optimistic bias, especially for events perceived as controllable.

Heerey et al (2008) studied DM impairments, in the context of reward sensitivity among individuals with SZ compared to non-ill individuals. They tested reward sensitivity by introducing random visual representations of faces with different shaped mouths (short, long, or no mouth). Participants chose between two simultaneous gambles involving monetary rewards or penalties involving the faces. There was no detection of any group differences in development of bias which suggests intact sensitivity to reward among individuals with SZ. Individuals with SZ placed less influence on the potential losses when compared to the non-ill individuals suggesting there may be deficits in WM. The researchers concluded that individuals with SZ have intact implicit learning measures when coupled with reward. However, degraded WM compromises their ability to weigh outcomes during emotional DM (Heerey et al, 2008).

Disorganized thoughts and speech patterns are a hallmark of SZ and exist alongside impaired motivation and a marked difficulty in maintaining and pursuing long-term life goals.
Patients have poor accuracy on tests such as the well-used WCST, where participants learn and update card-sorting rules. SZ patients fail to acquire even the first sorting rule and this is not due to a general cognitive impairment. They often show high rates of perseverative errors, suggesting a difficulty in abandoning and updating a response pattern in the face of negative feedback.
Frith (1992) suggested that delusional thinking results from faulty inferences regarding the motives of other people. Also delusional thinking in SZ is closely related to impaired DM processes. It is suggested that delusion formation is linked to a particular pattern of performance on probabilistic DM tasks (Gateway & Freeman, 1999). Delusions might be due to a tendency to make inferences based on insufficient evidence (Huq et al, 1998). Consistent with an underlying deficit in inference, it has been shown that delusional symptomatology is related to "jumping to conclusions (JTC)" in reasoning tasks. Furthermore, SZ patients tend to show this pattern of behavior regardless of whether delusional symptoms are present at the time of testing (Fine et al, 2007). The task to demonstrate this is the so-called "urn" or "beads" task. Patients with SZ tend to make early decisions on this task, often making a decision after just one draw (Dudley et al, 1997, Fear & Healy, 1997, Moritz & Woodward, 2005). In contrast, healthy controls tend not to make a decision before five or six draws have been completed (Garety et al, 1991). It has therefore been suggested that making a decision at two items or fewer should be classified as JTC.
JTC seems to be specifically related to delusional ideation. But JTC can be detected in both deluded and non-deluded SZ patients compared to healthy and psychiatric controls (Moritz & Woodward, 2005). JTC is definitely a consistent finding in SZ.
WM might be impaired in patients who show JTC compared to those who do not. One other explanation for the JTC response style observed in SZ is that patients simply make decisions based on less evidence (liberal acceptance). Another explanation is that JTC manifests not through a lowered threshold for making a decision but through each piece of evidence being relatively "overvalued" (hypersalience of evidence).

JTC cannot be attributed only to dopaminergic overactivity, at least when induced acutely. The relationship is not linear. Probably chronic aberrations in DA firing are required for the emergence of JTC.

There is also some suggestion that poor emotion regulation might have a role to play. The involvement of areas such as the striatum, the dorsolateral prefrontal cortex, and the intraparietal sulcus in deciding on a probabilistic inference rather than continued evidence seeking (as in JTC) might be the case. These brain areas contribute to related DM tasks. Signaling in the dopaminergic striatum during reward prediction might also play a role in JTC behavior, as dopaminergic antipsychotic treatment abolishes JTC on an emotionally version of the urn task (Menon et al, 2008). In addition to the striatum, responses in the dorsolateral prefrontal cortex are also reduced in schizophrenics, compared to those in healthy individuals, when performing tasks requiring reward prediction (Weickert & Goldberg, 2009). Schizophrenics appear to show reward-related response reductions in many of the brain areas activated by the urn task in healthy participants. Dysfunctional interactions between the dopaminergic striatum and cortical areas, such as intraparietal sulcus and dorsolateral prefrontal cortex, might explain JTC behavior in SZ patients. In sum, JTC in SZ seems to be a consistent finding and there is strong evidence linking JTC to delusion formation.

Functional MRI studies have implicated a network involved in making urn choices, which includes striatal, insular, parietal, and prefrontal areas.

A large body of evidence has demonstrated significant cognitive dysfunction in SZ, which is associated with disorganization, negative symptoms, and impaired functional outcome. Information-processing deficits in SZ are described in attention, WM, inhibition, and context processing. Context-processing deficits are associated with WM impairments and dopaminergic tone in the prefrontal cortex (PFC). Both cognitive control and social cognition deficits are disease outcome predictors. Faulty information processing in schizophrenics translates into impaired risk assessment. Thus, patients with SZ exhibit global cognitive control dysfunction that is reflected in specific deficits in risk assessment, reward processing, and temporal discounting. All these impairments are translated in a devastating dysfunction in the disorder.

CHAPTER THREE – Sensorimotor abnormalities in SZ

General symptomatology

Catatonia, abnormal involuntary movements, neurological soft signs (NSS), psychomotor slowing are the most common motor deficits of the schizophrenics.

Bleuler estimated that more than 50% of SZ patients presented with either persistent or recurrent catatonic symptoms. He considered catatonia a nonspecific symptom of SZ. The cognitive symptoms (delusions, hallucinations, and disorders of self-perception) were considered primary. The motor and emotional symptoms were interpreted as secondary. When the antipsychotics were introduced, motor symptoms in SZ were attributed to the treatment. Many patients present with more than one motor symptom (Walther & Strik, 2012) (table 3.1).

Table 3.1 Motor symptoms in SZ (Walther & Strik, 2012, references in Walther & Strik, 2012)

	First episode medication naïve	First episode medicated	Chronic medication naïve	Chronically medicated
NSS (>1 symptom)	78–97% [51, 94]	48–100% [95, 96]	23% [97]	39–98% [52, 98]
Dyskinesia	12–13% [34, 99]	3% [57]	35–51% [33, 76]	29–100% [38, 56, 100]
Parkinsonism	18–27% [34, 75, 99]	34–43% [57, 73, 101]	15% [76]	23–55% [37, 38]
Catatonic symptoms (≥2 signs)	17% [67]	5% [57]	no data available	10–32% [49, 70]

Catatonia is defined as abnormal motor behavior which also includes impaired volition and affect. Up to 40 symptoms have been described as catatonic. Pure motor signs include posturing, mannerisms, immobility, stereotypies, catalepsy, grimacing, and waxy flexibility. Signs associated with volition include automatic obedience, negativism, withdrawal, and ambitendency. There is an inability to suppress complex motor activities, either self-initiated (rituals or stereotypies) or induced (echophenomena). Stupor, excitation, nudism, verbigeration, perseveration, staring, and vegetative instability have been interpreted as catatonic. In SZ, the most frequent catatonic symptoms are mutism, posturing, stereotypies, and mannerisms (Walther & Strik, 2012).

Parkinson's has 6 main clinical features: resting tremor, rigidity, bradykinesia, loss of postural reflexes, flexed posture and motor blocking (freezing). In SZ, muscle rigidity and bradykinesia are the most frequently reported parkinsonian signs. Parkinsonism of unmedicated first-episode patients deteriorates with antipsychotic treatment in some

patients (28%), while in others, remains unchanged (15%) or ameliorated (6%) with treatment. Spontaneous Parkinson's has been suggested to predict neuroleptic-induced Parkinson's (Walther & Strik, 2012).

Negative symptoms refer to the loss of affective experience and expression, as well as disturbances of volition, such as apathy and anhedonia. They may be associated primarily with SZ or may develop secondary to social deprivation or antipsychotic medication. The patients become less active. This "psychomotor poverty syndrome" is linked to negative symptoms and comprises decreased spontaneous movements and flattened affect. Morrens et al (2007) have reviewed reduced processing speed (psychomotor slowing, PS) assessed with RT and fine motor acts (drawing and writing). They found high prevalence of slowing, associated with negative symptoms, independent from antipsychotic medication (Morrens et al, 2007, Walther & Strik, 2012).

Dyskinesia and Parkinson's may co-occur in both chronic and first-episode SZ patients. Parkinsonism and retarded catatonia are highly correlated. Negative symptoms are highly correlated with catatonia, NSS, dyskinesia and Parkinson's.

NSS are associated with dyskinesia and Parkinson's, as well as with cognitive function. NSS refer to neurological abnormalities in coordination, sensory integration, and sequential motor acts. NSS tend to be stable over time and are prevalent in early stages (table 2.1). They appear to be independent of medication (Walther & Strik, 2012).

Tardive dyskinesias (TD) (abnormal, involuntary, repetitive movements of the orofacial, limb, trunk, and respiratory muscles) occur throughout the disease (table 2.1, Walther & Strik, 2012).

Neuropathology-Biochemistry

Neuropathological studies in SZ have focused on the limbic system, the hippocampus, and the dorsolateral prefrontal cortex. The results on neuron density in the premotor, motor, and anterior cingulate cortices (ACC) are inconclusive. Reduced synaptic density and aberrant wiring were found in the ACC. Brain volume reduction in BA area 24 (cingulate motor areas) was found. This indicated reduced neuron number and volume of the putamen and caudate. Reduced thalamus volumes were also found (Walther & Strik,

2012). The “disconnectivity hypothesis” of SZ suggests an important role for the white matter in the disease’s symptomatology. SZ patients demonstrate increased interstitial white matter neurons. This suggests deficient migration from the white matter to the cortex (Walther & Strik, 2012).

Disturbed GABAergic neurotransmission was found in brain regions, including the ACC and the primary motor cortex. The GABAergic reduced tone within the basal ganglia suggests that some motor symptoms are the result of GABAergic dysfunction in SZ (Walther & Strik, 2012).

Neurodevelopment

Large birth cohort studies indicated delayed gross motor milestones. Impaired motor skills before the age of 11 years in a proportion of children who later developed SZ were also found. Delayed neuromotor development and obstetric complications were shown to potentiate risk of SZ in adulthood. Deficits in motor coordination at the age of 10 were found to predict SZ 35 years later. Motor developmental changes and abnormalities in childhood which may predict adult SZ occur during the maturation of gray matter in the motor cortices and the motor network. During adolescence, increased pruning of dendritic spines contributes to the loss of gray matter in SZ (Walther & Strik, 2012).

The neurobiology of the motor system is linked with SZ at the level of neuronal structure, function, and chemistry in the premotor and motor cortices, basal ganglia and thalamus, as well as in the pathways connecting white matter. The above are consistent with the neurodevelopmental hypothesis of SZ.

The inferior parietal lobe (IPL), the temporal parietal junction (in both hemispheres) and the left hemisphere language areas are related to schizophrenic symptoms such as: auditory and visual hallucinations, abnormalities in facial gesturing, thought disorder, bizarre behavior, attentional deficits, delusions, thought broadcasting, insertion and withdrawal, social withdrawal, flat affect and aggressiveness.

Several experiments examined the functional circuits altered in SZ which involves parietal regions associated with sense of self. Functional brain connectivity changes were analyzed using fMRI in medicated schizophrenics and healthy controls. The functional connectivity

changes with the strongest links to SZ involved parietal instead of frontal regions (Teixeira et al, 2014). Most studies have focused though on brain tissue volumes. Neuroimaging may separate cortical area from cortical thickness. The most commonly reported findings are gray matter volume reductions in temporal and frontal lobes and increased volumes of the lateral ventricles. Most widespread cortical thinning is seen in frontal and temporal regions. More circumscribed thinning is found in occipital and parietal regions. However, cortical thinning in frontal and posterior temporal regions may not be specific to SZ (Rimol et al, 2012).

Schizophrenics versus healthy controls

Widespread reduction of cortical volume in frontal, temporal, occipital, and parietal regions is found in SZ.

The frontal lobe is affected (in both hemispheres), including lateral and medial superior frontal gyrus (SFG), middle frontal gyrus (MFG), inferior frontal gyrus, and orbitofrontal gyrus (OFG). In the left hemisphere, the medial OFG and the posterior lateral SFG were less affected.

Widespread temporal lobe regions in both hemispheres show significant reduction of cortical volume, including the entire inferior temporal gyrus and almost the entire ventral (fusiform and lingual gyri) and medial (entorhinal and parahippocampal gyri) temporal lobe. The entire medial temporal gyrus is affected in the right hemisphere and most of it is affected in the left hemisphere. Half of the superior temporal gyrus is affected in both hemispheres. Lateral and medial occipital lobes are also affected in both hemispheres.

Parietal regions show significant reduction of cortical volume in both hemispheres, including, laterally, the inferior parietal gyrus (IPG) and to a lesser extent the superior parietal gyrus, the posterior cingulate, isthmus cingulate, and precuneus. The supramarginal gyrus is mainly affected in the right hemisphere. Cortical area shows significant reductions in the frontal, temporal, occipital, and parietal regions in both hemispheres, generally less widespread than the cortical volume reductions (Rimol et al, 2012, fig.3.1).

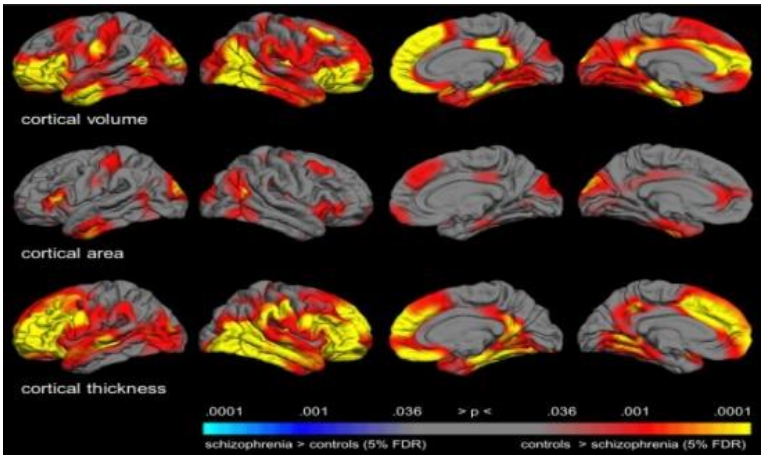


Fig. 3.1. Maps show significant differences between healthy control subjects and patients with SZ. The maps were produced from general linear models with cortical volume, area, or thickness as dependent variable at each location across the surface, covarying for age and sex (Rimol et al, 2012)

Rimol et al (2012) observed widespread reduction of cortical volume in frontal, temporal, occipital, and parietal regions in schizophrenics, compared to healthy controls. This volume reduction was mainly due to cortical thinning (fig. 3.1). Reduced cortical area in more circumscribed frontal, temporal, parietal, and occipital regions was also found. The generally low correlation between cortical area and cortical thickness is consistent with the theory that cortical area reduction and cortical thinning are independent processes. Cell death, synaptogenesis, synaptic pruning, and myelination strongly influence cortical thickness during the first two decades of life and continue to influence it throughout the life span.
Both functional and structural MRI studies found pathology in all these regions which may contribute to disrupted sensory perception in SZ. Smiley et al (2012) used postmortem samples from the left and right IPL, in order to compare the thickness and volume of the upper (I–III) and lower (IV–VI) cortical layers. The samples were divided into supramarginal and angular gyri, and neuron density and size were measured in the supramarginal gyrus. The laminar thickness and volume measurements did not demonstrate significant changes in SZ, but did show that the angular gyrus was thinner than the supramarginal gyrus, due to a difference mainly in the lower layers. Measurements of cortical thickness, neuron size and neuron density show hemispheric differences. Reduced cortical thickness is prominent in the upper layers but is not accompanied by changes in neuron density or size (Smiley & Falchier, 2009, Smiley et al, 2009, Smiley et al, 2012, fig 3.2).

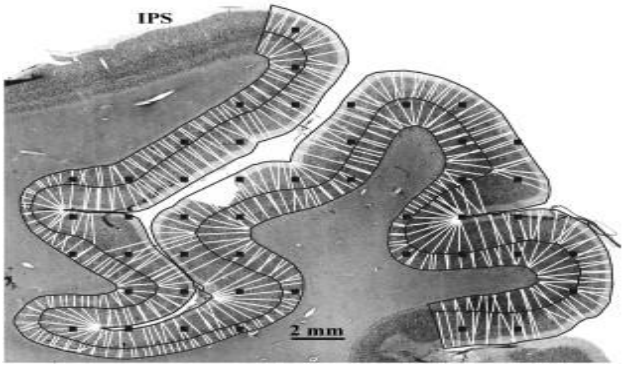


Fig 3.2 Laminar volumes and thickness were measured. Photomontages with resolution of 146 pixels per mm were made of each section, and interactive software was used to outline the borders on each photomontage of the pial surface, the layer III/IV border, and the white matter border (black lines). Measurements extended from the crest of the intraparietal sulcus (IPS) dorsally, ventrally to the crest of the lateral fissure, or in more caudal sections onto the gyrus ventral to the superior temporal sulcus. The "upper layer fractional volume" of each sample was the summed upper layer areas from all sections divided by their upper plus lower areas. Thickness of the upper and lower layers was measured by software that found the shortest distance between each border (white lines), displayed the measurements on colored maps, and estimated regional widths by summing the colored pixels in regions of interest on the flat-maps. Neuron densities were estimated by the optical disector method, using a randomly placed grid pattern of disectors (black squares) (Smiley et al, 2012)

Neuron density and size were measured in the supramarginal gyrus, in the identical regions of cortex used to measure cortical thickness (fig.3.3, 3.4).

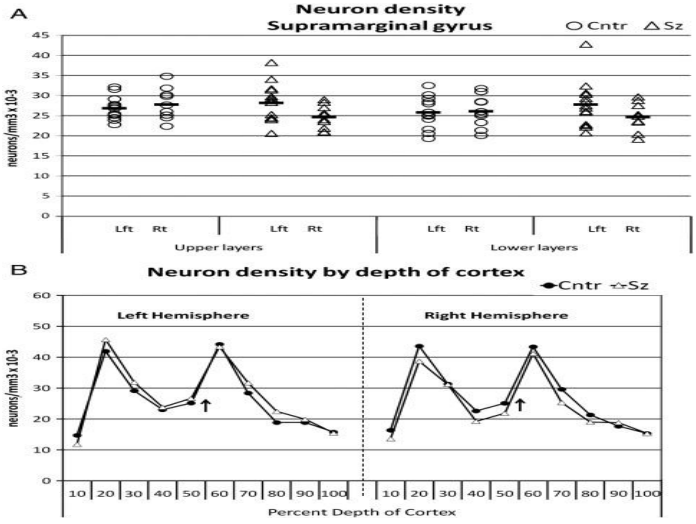


Fig.3.3. Neuron density was measured in the supramarginal gyrus. A. Compared to nonpsychiatric brains, the SZ sample had increased density in the left hemisphere, and decreased density in the right hemisphere, but the altered hemispheric asymmetry was not significant. B. Neuron density measurements were further plotted by percent depth of cortex. Depth of cortex was measured using the same approach as cortex thickness measurements; i.e., by finding the shortest distance from each disector site to each nearest laminar border. The arrow shows the border between the upper and lower layers. The plot is slightly distorted, as equal numbers of bins are given to the lower and upper layers, but the lower layers are only about 45% of the total cortex width. These plots provide qualitative view of the distributions, but individual bin values lack sufficient sampling density to provide statistically robust group comparisons. Circles = controls, triangles =SZ subjects (Smiley et al, 2012)

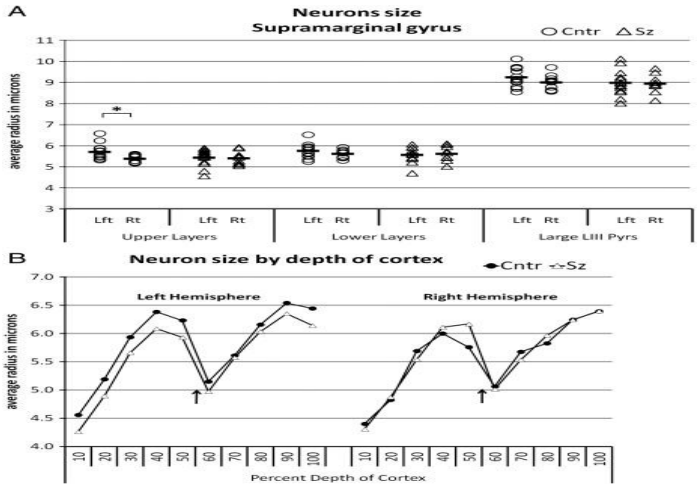


Fig.3.4. Neuron size was measured in the supramarginal gyrus. A. There was a significant layer × hemisphere interaction. Follow-up analysis showed a left>right asymmetry in the upper layers of the non-psychiatric sample (*p < 0.05, or 0.09). Large layer III pyramidal cells (LIII Pyrs) did not show more pronounced diagnostic or hemispheric differences than the other upper layer neurons. B. Neuron size measurements were further plotted by percent depth of cortex. The arrow shows the border between the upper and lower layers. The plot is slightly distorted, as equal numbers of bins are given to the lower and upper layers, but the lower layers are only about 45% of the total cortex width. Circles = controls, triangles = SZ subjects (Smiley et al, 2012)

The authors provide evidence for normal hemispheric asymmetry of the supramarginal gyrus, with larger neurons and slightly lower neuron density in the left hemisphere. Thus, SZ is associated with small anatomical changes in the IPL. Hemispheric differences in cell size and density seem consistent with findings in the temporal lobe (Smiley et al, 2012).

As already mentioned, SZ involves the prefrontal, temporal, and inferior parietal neocortical areas and the closely linked hippocampus, amygdala and septum in the limbic system. These structures form “an integrated network of neural systems and damage at a single location could cause widespread dysfunction. Any location in this network could be considered a site of the lesion in SZ (Torrey et al, 2007). Thus, SZ is not a disorder of a single brain area but a disorder of brain networks. The superior longitudinal fasciculus, connecting the frontal and parietal areas, is among the tracts exhibiting abnormalities. Studies have reported altered white matter integrity in the tracts connecting the frontal cortex with the temporal and parietal cortices (Torrey et al, 2007).

Disruption of sensory integration is one of the earliest and most common symptoms of SZ. Perceptual dysfunction is the most invariant feature of the early stage of SZ and is found in almost two-thirds of patients. Thought disorder is probably also explainable as a defect in the

sensory integration system of the IPL and other parts of the association cortex (Torrey et al, 2007). Passivity phenomena in SZ may be associated with hyperactivity in the parietal cortex, perhaps lateralized to the right hemisphere.

Executive functions

Executive functions are considered to be primarily associated with the prefrontal cortex. The functions of prefrontal cortex are understood with reference to its connections with other structures, including the parietal cortex. Multiple executive functions, such as the Wisconsin Card Sort Test (WCST), activate the IPL in addition to prefrontal areas (Torrey et al, 2007). Executive functions impaired in individuals with SZ may be due to dysfunction in the IPL and the prefrontal cortex.

Attention is known to be impaired in many individuals with SZ. Mesulam & Geschwind (1978) noted that "a lesion in the inferior parietal lobule may result in a similar disconnection of cortex from the limbic system" and produce attention deficits. An MRI study of neuroleptic-naïve individuals with SZ using the Continuous Performance Test (CPT) as a measure of sustained attention reported significant correlations between CPT performance and gray matter volume in the left supramarginal and angular gyri (Salgado-Pineda et al, 2003). Working memory (WM), also known to be impaired in SZ, involves the IPL too. Using fMRI, Kindermann et al (2004) reported diminished WM response in schizophrenics in the left supramarginal gyrus (BA 40) as well as in other regions. Jansma et al (2004) also carried out a fMRI study of WM in SZ and found that the supramarginal gyrus was bilaterally involved (Torey et al, 2007).

There is also frequent association of stereoagnosia and tactile apraxia which shows the mutual interdependence of the sensorimotor processes involved in active touch. In addition, parietal lobe function is critical for the control of force and posture and for the formation of the body image with its relation to external space (guidance of movements, including the eyes). Imaging studies show the prominent role of the parietal cortex as a sensorimotor interface. They provide complementary information about the interrelationship between perception and action. Action observation activates the premotor cortex, but the parietal cortex is also

recruited whenever an action involves objects. This emphasizes the significance of the parietal cortex for object-directed motor behavior (Freund, 2003).

We have two separate visual pathways, a magnocellular system that is most closely related to the ancestral mammalian visual system and a parvocellular system with unique sensitivity to wavelength (color) of light and the ability to produce high-resolution visual images (fig 3.5).

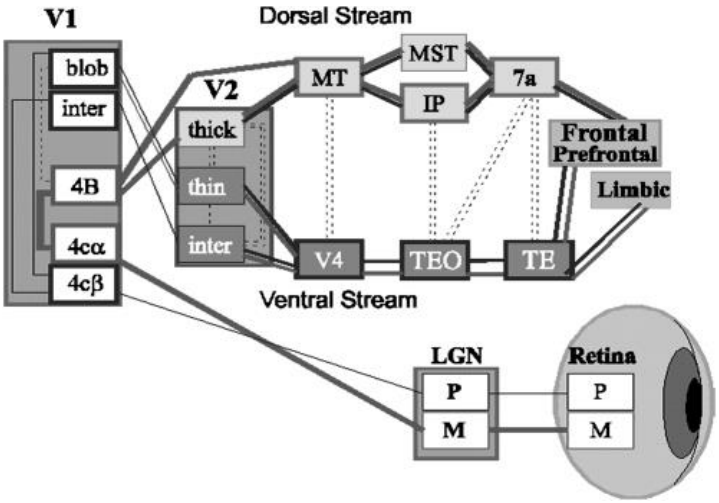


Fig.3.5. Schematic representation of the human visual system. The magnocellular (M) system and the dorsal stream projection pathway are shown with thick lines. The parvocellular (P) system and ventral stream projection pathway are shown with thin lines (Javitt, 2009)

The parvocellular system extracts more information but functions more slowly than the magnocellular system. It is concentrated foveally and engages only limited portions of the complex visual scene at any time. The magnocellular system guides parvocellular processing. Thus, it provides a general low-resolution “frame” for the visual environment, which is then “filled in” by details from the slower parvocellular system.

In SZ, physiological deficits affect functioning of the magnocellular visual pathway, which relies on NMDA-based mechanisms. The parvocellular system may show impairments as well. Impairments in early visual processing are well documented in SZ (Javitt, 2009). Thus, visual dysfunction occurs in SZ. Reviews of the neurophysiological literature regarding visual function conclude that deficits most likely represent interplay among magnocellular and parvocellular systems and occur at multiple levels. As the magnocellular system conducts more rapidly than the parvocellular system, humans show a “global advantage” (they focus on the overall structure of a visual scene (the “forest”) before they focus on the fine details (the “trees”). Loss

of the normal global advantage is consistent with dysfunction of magnocellular systems in SZ (Javitt, 2009). Early visual deficits also contribute to impairments in visual depth perception in individuals with SZ. Deficits in early visual processing, involving the magnocellular system, interfere with the ability of patients to read visual expressions (Javitt, 2009).

Bottom-up vs top-down models

Sensory dysfunction and its impact on the cognitive impairment in SZ is easiest to conceptualize as “bottom up” vs “top down.” The neurocognitive dysfunction in SZ is best though understood as “generalized” vs top down. It is clear that bottom-up sensory dysfunction may be a bottleneck. For example, “social cognition” depends upon the ability to interpret facial expressions and tone of voice. If patients cannot accurately process faces because of early visual deficits, or process the pitch changes that allow one to interpret the tone of voice, trying to remediate social cognition is useless. If the patients experience the world around them differently, they will react to it differently as well (Javitt, 2009).

Information processing

Information processing defines the sequence of operations to stimuli that occur in the CNS. Theories initially stressed that stimuli were normally processed in a series of steps or "stages" that corresponded to operations performed at different levels and locations in the CNS. Stimuli were thought to be processed and encoded in a way that facilitated perception, memory and information of the outside world. Schizophrenics were thought to have blocks or abnormalities in the early stages of information processing. This was followed by a cascade of "downstream" effects on cognition and social functioning (Braff, 1993).

More recently, information processing is interpreted in terms of parallel and complex channels rather than in terms of serial and simpler stage models (Edelman, 1987). Computer models are being constructed. They rely on the network theory (neurons from multiple loci that fire in an integrated array of time). These coordinated events are impaired in SZ patients (Braff, 1993).

Attention

Involuntary attention is linked to the natural valence that a stimulus has for an individual (Braff 1993). It seems to be plastic and changeable. But writing or reading a difficult book is an attention demanding task that forces the individual to direct a voluntary, effortful attention on

a specific topic. Voluntary attention and vigilance must be consciously and continually focused on the task at hand. The two attentional modes (involuntary and voluntary) form a continuous form of cognitive processing (Braff, 1993). It is believed that SZ patients have an attentional deficiency that can be characterized as specifically impairing conscious, serial, and by limited channel capacity operations. In contrast, automatic (unconscious) processes often appear to be spared in SZ patients. The limited channel capacity processes, characteristic of controlled serial systems, are disordered in SZ. In contrast, parallel processes seem to be less impaired in SZ patients.

Integration of information processing and attentional theories

Broadbent's (1958) idea was that sensory input is mediated by a single, limited capacity channel. Treisman (1969) added the concept of “filtering” and "functional channels" which were actively selected for processing. This is not true for all data processing in SZ.

Kahneman (1973) showed that the processing of a second stimulus did not always wait until the analysis and the response to the first stimulus, indicating that multiple channels and processes of selection are involved in simple tasks (Braff, 1993). Deficient processing resources in SZ patients may result from excess stimulation due to sensory flooding, a smaller pool of resources, or an inability to mobilize and allocate resources.

Reaction time (RT)

Research in RT is extensively reviewed by Nuechterlein (1977). Investigators use the regular and irregular forms of the RT task, which Shakow and his colleagues used so widely (see Nuechterlein 1977, chapter 4). The regular and irregular forms of the RT task use uniform and varied preparatory intervals between a warning signal and the imperative stimulus. Even relatively cooperative schizophrenics showed slower RTs and an inability to benefit from the regular and predictable preparatory intervals. Rodnick and Shakow (1940) demonstrated that the "set index" was sensitive in discriminating SZ-linked deficits in RT. The “set index” was designed to minimize superficial attentional artifacts and to identify a more core deficit in SZ patients' attentional performance. Rodnick and Shakow (1940) believed that the “set index” minimized the contamination of schizophrenic performance by potential artifacts such as poor

levels of cooperation or motivation or both. It turned out, however, that high scores on the "set index" were not unique to schizophrenics (Nuechterlein 1977, Braff 1993, also chapter 4).
It is quite possible that RT techniques, in combination with other tasks of information processing and cerebral activity (PET), may yield important new information.

Psychomotor functioning in SZ

Clinical presentation of slowed psychomotor functioning

In clinical practice, schizophrenics are slowed in their responses or in their movements. In more severely affected patients, movements can be extremely slow and psychomotor activity is sometimes reduced to the minimum, affecting negatively social interactions and daily life activities. Both gross and fine motor performances have been reported to be affected. In addition to slowed actions, a reduction in the quantity of psychomotor activity is also observed, sometimes recognized as negative symptoms. The diminished psychomotor activity was also labelled the "psychomotor poverty syndrome", including poverty of speech, decreased spontaneous movements, and blunting of affect (Morrens et al 2007).

Assessing psychomotor speed

Neuropsychological tasks are used to assess psychomotor slowing (PS) in schizophrenics (table 3.2). These tests address psychomotor and other cognitive functions in time-limit conditions, and they are either more focused on processing speed or on psychomotor speed.

- **Table 3.2 Overview of studies addressing PS in SZ (Morrens et al, 2007, references in Morrens et al, 2007)**

Study	Sample (*n*)	Mean Age	Inpatient/Outpatient	Medication	Psychomotor Task	Main Findings
Caligiuri et al	Neuroleptic-naive schizophrenic patients (24)	42.2	14 inpatients and 10 outpatients	/	Wrist rotation	12% of neuroleptic-naive schizophrenic patients had bradykinesia compared with none of the healthy controls.
	Healthy controls (24)	42.2				
	Schizophrenics (12)	29.3				
Carnahan et al	Healthy controls (12)	26.1	?	Antipsychotics	Fitts' task with mouse on graphics tablet	Relative to the healthy controls, the patients exhibited a movement-planning deficit without a decrement in movement execution. The patients still performed according to Fitts' law, which states that in aiming movement time decreases as target distance decreases and target size increases.
Fuller and Jahanshahi	Schizophrenics (11)	38.5	Outpatients	Antipsychotics	Purdue pegboard task and FTT	Patients were slower than the controls in both tasks in the unimanual but not in the bimanual condition. Peg
	Controls (13)	38.15				

Study	Sample (*n*)	Mean Age	Inpatient/Outpatient	Medication	Psychomotor Task	Main Findings
						placing was less slowed when performing a secondary task with the other hand. Pegboard and FTT performance significantly correlated with negative symptoms.
Gallucci et al	Schizophrenics (20)	31.1	?	2 unmedicated, 12 AAP, 6 CNL, and 4 anticholinergics	Handwriting movements recorded with graphics tablet	Handwriting in patients was not slowed but less efficient and consistent with a trend toward macrographic strokes.
Henkel et al	Schizophrenics (16)	35.1	Inpatients	Test-retest: drug-free vs haloperidol (mean dose: 10.4 mg) and anticholinergics (*n*= 6)	Drawing of circles and writing of sentences on writing tablet	Performance of neuroleptic-free patients was slower. Slowing was associated with negative symptoms. Amelioration of negative symptoms under haloperidol treatment was significantly associated with speeding-up of handwriting.
	Healthy controls (16)					
Holthausen et al	Schizophrenics (32)	24.8	?	Average dose: 6.1 mg haloperidol equivalents, 7 drug-free patients, and 15 on anticholinergics	FTT	FTT correlated with the depressive and the negative symptom dimension.
	Schizophreniform (10)	23.7				
	Delusional disorder (2)	28.5				
	Brief psychotic disorder (2)	18.0				
	Psychotic disorder NOS (4)	31.8				
Jogems-Kosterman et al	Schizophrenia (19)	37.0	14 outpatients	Antipsychotics (mean dosage 7.6 mg haloperidol equivalents)	Line-copying task, complex-figure copying task recorded on writing tablet	Patients' movement initiation and execution was slowed. Overall, patients were one-third slower than the controls. Initiation time latencies with increasing complexity were significantly higher in the subgroup with higher negative symptoms. Increased reinspection times demonstrated affected planning strategy.
	Controls (19)	37.5				
Malla et al	Schizophrenics (21)	29.0	?	Antipsychotics	Fitts' task with mouse on graphics tablet	Weak correlations between psychomotor poverty and RTs and no correlations with movement times. Strong associations between RT and disorganization syndrome.
Mohamed et al	First-episode schizophrenics (94)	26.1	Inclusion after admission	73 neuroleptic-naive patients, 14 receiving antipsychotics for less than a week, 7 for less than 2 wk	FTT	Impairments in speeded cognitive tasks with (SDST, and TMT) and without (Stroop) motor component. Patients performed relatively better on the FTT, leading the authors to conclude that poor performance on speeded tasks reflects bradyphrenia rather than bradykinesia.
	Normal controls (305)	25.5				
Morrens et al39	Schizophrenics (30)	27.5	Inpatients	Atypical antipsychotics (22), conventional	SDST on graphics tablet	Both matching time (initiation) and writing time (execution) on SDST were slowed but
	Controls (30)	33.0				

Study	Sample (*n*)	Mean Age	Inpatient/Outpatient	Medication	Psychomotor Task	Main Findings
				neuroleptics (7), and other psychotropics		unassociated. Matching time, reflecting slowing in higher order cognitive processes, but not writing time, reflecting PS, proved associated with other neuropsychological measures.
Putzhammer et al	Drug-naive schizophrenic patients (25) Schizophrenic patients treated with CNL (16) Schizophrenic patients treated with AAP (25) Healthy controls (25)	/	?	In addition: 14 patients lorazepam and 12 patients biperiden	Movement analysis of gait	Relative to the healthy controls, all patients exhibited decreased gait velocity due to shorter stride length while cadence (steps per minute) was not affected. Conventional antipsychotics intensified the problem, whereas atypicals did not cause additional gait disturbances.
Putzhammer et al	Drug-naive schizophrenic patients (14) Schizophrenics treated with CNL (14) Schizophrenics treated with olanzapine (14) Healthy controls (14)	36 38 35 46	Inpatients	In addition: 8 patients in total lorazepam and 5 patients in total biperiden	Movement analysis of gait	Compared with the healthy controls, all patients had decreased gait velocity due to shorter stride length. The most striking difference was observed between the patients on CNL and the controls. Impaired gait parameters can be normalized in schizophrenic patients by external stimulation via treadmill walking.
Schroder et al	Schizophrenics (12) Healthy controls (12)	28 27	?	9 clozapine, 2 conventionals+ biperiden, and 1 drug free	Pronation/supination device during fMRI	No differences in measures of motor retardation (repetition rate and amplitude) between patients and controls. Variability was significantly increased in the patients and activation of sensorimotor and SMA cortices was significantly decreased.
Tigges et al	Schizophrenics (27) Healthy controls (31)	31.0 33.3	Inpatients	13 drug free and 14 CPZ-eq: 507 mg	Handwriting on writing tablet	Patients had longer stroke durations and decreased automatization. Stroke length and velocity were less regular in the treated patients. Stroke-length irregularity was higher in patients treated with atypicals and not with typicals. Positive and negative symptoms had little relation to the handwriting measures.
Van Hoof et al	Schizophrenics (20) Depressed patients (20) Healthy controls (20)	39.9 47.0 43.1	Inpatients	CPZ-eq = 710	SDST on a writing tablet	The depressed patients demonstrated an overall slowing in matching and writing times, whereas the schizophrenic patients only displayed prolonged matching times in comparison with both the depressed patients and the healthy controls.
Yang et al	Schizophrenics (28)	29.3	19 outpatients and 9 other (?)	19 neuroleptic treatment and 9	FTT	The FTT showed the strongest correlation with D2 receptor

Study	Sample (*n*)	Mean Age	Inpatient/Outpatient	Medication	Psychomotor Task	Main Findings
				medication free		binding, while the WCST and attention test had no correlation with D2 receptor binding.

- *Note*: AAP = atypical antipsychotics, CNL = conventional neuroleptics, CPZ-eq = chlorpromazine equivalents, FTT = finger-tapping test, SDST = Symbol Digit Substitution test, SMA = supplementary motor area, TMT = Trailmaking Test, WCST = Wisconsin Card Sorting Test, RT = reaction time, PS = psychomotor slowing, and NOS = not otherwise specified (Morrens et al, 2007, references in Morrens et al, 2007)

Schizophrenics are significantly slowed compared with healthy controls, even when they copy a simple line or familiar figures (Morrens et al, 2007).

Gross motor tasks

There is evidence for decreased gait velocity in neuroleptic-naive schizophrenics which results from reduced stride length rather than from step frequency (Morrens et al, 2007). The gait disturbances worsen as a cause of conventional but not atypical antipsychotic treatment.

Reaction-time (RT) paradigms

RT paradigms in SZ have systematically shown responses to be impaired. RT trials involve the rapid initiation of responses that are elicited by external cues.

Although they also have a psychomotor, executive component, RT paradigms are mainly sensitive to deficits in vigilance and processing speed.

PS and other symptoms

Slowing and positive symptoms

Morrens et al (2007) found the initiation and execution of the copying movement of a simple line to be correlated to the severity of positive symptoms. Processing-speed tasks have not yielded significant relationships with the severity of positive symptoms. A correlation between decreases in RTs and reductions in positive symptoms after antipsychotic treatment was found (Morrens et al (2007).

Slowing and negative symptoms

Processing-speed and psychomotor tasks are associated with negative symptoms or Liddle's psychomotor poverty syndrome in various studies (table 3.4). Henkel et al (Morrens et al, 2007) found negative symptoms in unmedicated patients to be significantly related to lower velocities for drawing movements. After treatment with haloperidol, the improvement of

negative symptoms was significantly correlated with a speeding-up of drawing. Using a drawing task executed on a graphics tablet, Malla et al (Morrens et al, 2007) found that the patients' movement times were not related to any of the symptoms but that their RTs were correlated with psychomotor poverty and disorganization. Associations between psychomotor poverty and slowing in a simple RT task in patients with persistent but not with remitting illness has been shown (Morrens et al, 2007).

The clinical course of PS

PS has been found in adolescents with SZ spectrum disorders as well as in unmedicated patients early in the course of the illness. Performance has also been linked to familial risk of SZ, suggesting that PS may be familially transmitted (Morrens et al, 2007). One longitudinal study explored the evolution of PS in SZ. A group of first-episode or recent-onset patients was administered a series of cognitive tasks at index hospitalization and again after 5 years. They exhibited stable or improved performance on all cognitive tasks, except on the finger-tapping test, the performance of which was highly significantly worsened at the 5-year follow-up (Morrens et al, 2007).

PS and patients' outcome

Morrens et al (2007) mentioned that clinically observable PS in schizophrenic patients to be the strongest predictor of re-hospitalization.

Rapid fingertip movements and speeded manual manipulations have been shown to predict the patients selected for rehabilitation programs. Using drawing tasks, researchers found that both schizophrenic in- and outpatients exhibited slowed movement initiation but that only inpatients showed slowed movement execution as well. It was suggested that the severity of motor dysfunctioning could predict prognosis with greater motor impairment indicating a more severe course of the illness and poorer treatment outcome (Morrens et al, 2007).

It was found that acute schizophrenics who had faster RTs at admission had a moderately significant tendency for showing greater clinical improvement after a brief hospital stay (3–4 months) than patients with slower RTs.

The overall level of RT reflects an individual's "environmental responsivity," a critical factor for recovery.

Antipsychotics and slowing

Although early studies found that treatment with conventional neuroleptics cause impairment in psychomotor functioning, later reports yielded less consistent findings. Recent studies demonstrated improvement of psychomotor functioning after both atypical and conventional antipsychotic treatment (tables 3.3 and 3.4, Morrens et al, 2007).

Table 3.3 Tasks assessing processing speed and psychomotor performance showing associations with negative symptoms or Liddle's psychomotor poverty in cross-sectional and longitudinal studies

Neuropsychological Tasks and Studies

Cross-sectional studies

- Processing-speed tasks
  - Trailmaking test
  - SDST
  - Slower responses on 2-choice guessing task
  - Prolonged critical interstimulus interval in the backward masking task130
  - Reaction-time paradigms
- Psychomotor tasks
  - Pegboard task, finger tapping
  - Drawing tasks (M. Morrens et al, unpublished data)

Longitudinal studies

- Processing-speed tasks
  - SDST and verbal fluency
- Psychomotor tasks
  - Drawing task

- *Note*: SDST = Symbol Digit Substitution Test (Morrens et al (2007)

Table 3.4 Double-blind controlled trials investigating antipsychotic effects on PS in SZ

Study	Diagnosis	Subjects	Mean Age (y)	Sample Size	Trial Duration (wk)	Medication Groups + Mean Dose Ranges	Psychomotor Measures	Main Findings
Kern et al	Schizophrenia	Treatment resistant	40	56	8	Risperidone (6–7 mg/d) and haloperidol (15–19 mg/d)	Pin test and pursuit rotor	Patients on risperidone performed significantly better on pin test. No significances on pursuit-rotor task.
Purdon et al	Schizophrenia	Within 5 y of first neuroleptic exposure	29	65	52	Olanzapine (5–20 mg), haloperidol (5–20 mg), and risperidone (4–10 mg)	Grooved Pegboard and FTT	Within group: improvement with olanzapine on pegboard. Between group: olanzapine > haloperidol on both tasks, olanzapine > risperidone on pegboard.
Purdon et al	Schizophrenia	Chronic patients	34	25	26	Quetiapine (468.2 mg/d) and haloperidol	FTT and Grooved Pegboard	Only 11 patients completed the full study. No significant

Study	Diagnosis	Subjects	Mean Age (y)	Sample Size	Trial Duration (wk)	Medication Groups + Mean Dose Ranges	Psychomotor Measures	Main Findings
						(15.5 mg/d)		differences between and within groups on any of the psychomotor measures.
Bilder et al	Schizophrenia and schizoaffective disorder	Treatment resistant	41	101	14	Clozapine (452 mg/d), haloperidol (19.6 mg/d), olanzapine (20.2 mg/d), and risperidone (8.3 mg/d)	FTT	Significant improvement over time for clozapine for fine motor functioning factor. No group × time interactions.
Green et al	Schizophrenia and schizoaffective disorder	Stable outpatients	43	62	104	Risperidone (6.1–5.7 mg/d) and haloperidol (5.2–4.5 mg/d)	Pin test	Pin test was part of memory and fluency factor in analysis. No between-group differences in any of the cognitive cluster scores.
Keefe et al	Schizophrenia, schizoaffective disorder, and schizophreniform disorder	First-episode patients	24	167	52	Olanzapine (9.6–11.3 mg/d) and haloperidol (4.6–4.8 mg/d)	FTT	No improvement in either medication group after 12 or 52 wk.
Keefe et al	Schizophrenia and schizoaffective disorder	Chronic in- and outpatients	39	414	52	Olanzapine (*n* = 159), risperidone (*n* = 158), and haloperidol (*n* = 97)	Grooved Pegboard	Significant improvement in the risperidone and olanzapine groups but not in the haloperidol group at 52 wk.

- *Note*: FTT = finger-tapping test and PS = psychomotor slowing (Morrens et al (2007, references in Morrens et al, 2007)

Our knowledge of the neurobiology of slowed functioning is limited. Only few studies have investigated the associations between performance on the tasks and the electrophysiological or radiological markers of brain functioning.

CHAPTER FOUR - Reaction time (RT) studies in schizophrenia (SZ)

Many studies reported the slowness of response characteristic of schizophrenics on the RT task. The first investigations took place at the Worcester State Hospital by Shakow and his colleagues in 1972. They reported that chronic schizophrenics were slower than controls in simple RT. Shakow's study contained regular and irregular series of preparatory intervals (PIs). Regular series involved the presentation of a block of RT trials with identical PIs between warning signal and imperative stimulus. Irregular series consisted of randomized presentations of several different PIs. The regular series allow the subject to learn when to expect the imperative stimulus and to prepare to respond quickly to it.

Huston et al (1937) found that the chronic schizophrenics were significantly slower than controls in responding to each of six PIs ranging from 0.5 to 10 seconds whether part of a regular or an irregular series. In addition, schizophrenics, unlike controls, were unable to improve their RTs in regular as compared to irregular series when the PI exceeded 2 seconds. Rodnick & Shakow (1940) using a simple visual RT task with preparatory intervals of 1, 2, 4, 7.5, 15, and 25 sec, replicated the above study. Schizophrenics though failed to benefit from the regular as compared to the irregular presentation after the 4-second PI rather than the 2-second PI.

A "set index" was proposed to provide a high degree of separation of chronic schizophrenics and controls (Tizard & Venables, 1956). Zahn & Rosenthal (1965) found that on the "set index", acute schizophrenics significantly differed from both the non-schizophrenic patients ($p<.05$) and from a chronic schizophrenic sample ($p<.01$). They concluded that the overlap between acute schizophrenics and non-schizophrenics was considerable. They also suggested that the index was not applicable for diagnostic purposes. High scores on the index were not unique to schizophrenics. They were though more characteristics of schizophrenics.

Preparatory intervals (PIs) in regular series

Shakow et al (1950) examined the regular and irregular series of RT trials as separate phenomena. They thought that the task set for the longer PIs was more difficult than for the short PIs. The longer time period increased the likelihood that various distractions would interfere with the "major set" (Shakow, 1950). There was a steep increase in RT of

schizophrenics with increasingly long PIs in regular series. Zahn et al (1961) introduced a condition in which the PI remained short (2 sec) but the interstitial interval (ITI) was lengthened substantially (to 14 sec). The pacing of the imperative stimuli was thereby matched to that of a long PI with the usual short ITI (a 12-sec PI with a 4-sec ITI). They demonstrated that the short PI with the long ITI did not lead to significant slowing, but the long PI with the standard ITI did lead to slowing for 26 chronic schizophrenics. The difficulties experienced by the schizophrenic trying to maintain a set during the longer intervals may lead to "withdrawal". The patient's general level of arousal would be affected to a greater degree by a series of long PIs.
Tizard & Venables (1956) showed that the RT-PI relationship characteristic of chronic schizophrenics was due to the general slowing of RT. Shakow thought that RT-PI relationships reflected deficient attention (Nuechterlein, 1977).

PIs in irregular series

Chronic schizophrenics showed the opposite RT-PI relationship for the irregular procedure than for the regular procedure. The schizophrenic group reacted most slowly on the shorter PIs and faster on the longer PIs compared to the controls. In the irregular series, the shorter the PI, the more likely was that the PPI was a longer one and that the PPI-PI discrepancy was large. The strong influence of the PPI on chronic schizophrenics accounted for retardation of RT at the shorter PIs in the irregular procedure. Schizophrenics appear to allow the preceding trial to interfere exceedingly with the development of an optimal preparedness on the current trial. The maintenance of focused attention for the longer period was not impaired by the possibility that the critical stimulus might appear earlier. But it confirmed that the longer rather than shorter PPI had the most potent effect on schizophrenic RT (Nuechterlein, 1977).

Cross-modal stimulus shifts

Sutton and his colleagues examined the effects of sequential changes in another variable, the sensory modality of the stimulus. They employed four stimuli in two sensory modalities (red light, green light, high tone, and low tone) as imperative stimuli. These were presented in an irregular order, with the subjects instructed to respond as quickly as possible to each. They found that chronic schizophrenics were slowed significantly more than controls by cross-modal changes in stimuli but not significantly more by ipsimodal changes.

Zubin's neuronal trace mode

Zubin suggested a model based on the assumption that facilitating and inhibitory neural traces had greater duration in schizophrenics than in controls. The processing of a given RT stimulus was hypothesized to leave a facilitating trace for similar future stimuli and an inhibitory trace for dissimilar stimuli. Zubin cited that the neural substrates for attention and for suppression were closely intertwined. Thus, his theory of inhibitory traces for attention to non-present but potentially competing stimuli was supported. In the case of a series of ipsimodal and cross-modal stimuli, the facilitation or inhibition from previous stimuli was assumed to center on the modality variable, while for an irregular PI series, the focus was on PI duration.

Zubin stated that in the modality experiments, a stimulus identical to the previous one, results in the fastest RT, an ipsimodal stimulus in the next fastest RT, and a cross-modal stimulus in the slowest RT. This progression would parallel decreased facilitation and increased inhibition of the stimulus in neural pathways.

Schizophrenics have been shown in several studies to be disproportionately slowed in RT by such distracting stimuli, even in the instance of simple RT to a series of identical stimuli (Nuechterlein 1977). Zubin predicted that the repeated identical imperative stimuli created stronger cumulative facilitatory traces for schizophrenic than for normal individuals. Dissimilar stimuli, including irrelevant stimuli, were inhibited more strongly by schizophrenics than by controls (Nuechterlein, 1977). Hunt & Cofer thought that failures to maintain a major set were secondary to the apathy and the "withdrawal from reality."

Motivational manipulations

Buss (1966) argued that if the patients were undermotivated, the introduction of positive or negative reinforcers should result in greater improvement for schizophrenics than for controls. Healthy people are sufficiently motivated under baseline conditions and should be nearer their peak performance compared to schizophrenics. With reinforcers, patients may become equally fast in RT as controls. Praise or encouragement led to greater improvement for schizophrenics in simple RT and less improvement for schizophrenics than controls in complex RT. In no study did positive social reinforcement lead to equivalent RTs for schizophrenics and controls (Nuechterlein 1977). Data overall though, do not support a motivational explanation as a

substitute for attentional or inhibitory dysfunction for the more complex aspects of schizophrenic RT performance.

Exogenous stimuli

The tendency of the schizophrenic to respond to irrelevant stimuli suggests that deviant attention is the fundamental cognitive disorder in SZ. Shakow and McCormick (1965) found that compared to normal controls, chronic schizophrenics were significantly more retarded on the last single stimulus than on the previous paired one. Exogenous stimuli were more distracting to them. Normal subjects also showed an impairment but to a lesser degree. Normals may differ in the ability to utilize all relevant information rather than to screen out irrelevant stimuli.

McGhie-Chapman-Lawson: studies of distractibility

McGhie et al (1967) conducted experiments on schizophrenic distractibility. Irrelevant stimuli were introduced in a wide variety of perceptual, immediate memory, and psychomotor tasks- among the latter, simple RT. Schizophrenic, non-schizophrenic psychotics and normal subjects were administered tests, first under standard conditions and then with distracting stimuli. They used a visual and an auditory simple RT task, differing from the work of Shakow, since no warning stimulus was used. Instead, the interstitial interval was varied randomly between 5 and 10 seconds, creating a situation similar to but not identical with an irregular PI series. Schizophrenics were as usual significantly slower on the basic RT performance than controls. This was also evident for the other psychomotor tasks. However, the schizophrenics were more impaired than controls by both visual and auditory distraction on a visual RT task and by visual distraction on an auditory RT task. Auditory distraction with visual stimuli also resulted in significantly greater retardation for schizophrenics than for the non-schizophrenic psychotic group. McGhie et al (1965) interpreted their results with the assumption that selective and inhibitory sides of attention form a fundamental deficit in SZ (Nuechterlein, 1977).

Payne and Caird: studies on overinclusion

Payne and Caird (1967) administered simple and discrimination RT trials to samples of paranoid and non-paranoid schizophrenics, and non-schizophrenic psychiatric patients. According to Payne's theory that overinclusion is the primary cognitive deficit in SZ, irrelevant stimuli should interfere with RT more for overinclusive schizophrenics than for those mainly characterized by

retardation. Payne thought that overinclusive thinking resulted from some defective "filter" mechanism which screened out irrelevant stimuli and made overinclusive patients very distractible in the RT situation. A simple RT task for such patients should become a discrimination RT task, because irrelevant stimuli, instead of being "screened out" when they occurred, are attended to and "processed" along with the relevant stimulus. Thus, RT would be delayed. Also, in a multiple choice RT task, overinclusive subjects would behave as if they were processing more information than that conveyed by the stimulus. Irrelevant stimuli would not be screened out but would also be processed along with the relevant stimuli.

Broadbent: information-processing model

Broadbent (1971) investigated the response selection which occurs beyond the filtering level. Broadbent's model distinguishes between filtering and pigeonholing aspects of information processing. Filtering refers to the process that determines what input to the limited capacity channel, will result from each stimulus. Pigeonholing refers to rules linking this input to “category states”. In this model, the filter acts only to weight the various inputs. The response selection or pigeonholing mechanisms is influenced by the full range of impinging stimuli. Output is dependent on the combination of filtering and pigeonholing processes, each operating on different stimulus characteristics (Nuechterlein, 1977).

Simple versus choice RT

Studies on choice RT in SZ initially involved a comparison of simple and choice RT. The theories of McGhie and Chapman (1961), Broen and Storms (1967), and Yates (1966) (Nuechterlein, 1977) are the best known. The stimulus complexity should be especially impairing according to McGhie and Chapman. Response competition is central to the schizophrenic deficit for Broen and Storms. Yates's (1966) theory parallels that of McGhie and Chapman (1961) but differs in two basic points. Yates postulates that a slowing of information processing is sufficient to explain the McGhie and Chapman findings, without the primary defect in either the selective filter or the short-term memory that McGhie & Chapman suggested. Yates, employing Broadbent's (1958) model, argues that schizophrenics are deficient in their processing of relevant information due to this slowness. Yates feels that McGhie & Chapman's emphasis on intrusion of irrelevant stimuli is unnecessary. Karras (1967) interpreted Yates's model to imply

that (1) both simple and choice RT should be longer for schizophrenics than controls and (2) schizophrenics should be slowed to a greater amount in choice as opposed to simple RT. All studies found that choice RT was slower than simple RT for schizophrenics (and controls).

Choice RT with multiple levels of complexity

Venables developed an equation relating complexity and RT. This equation is: RT = a + b log n, where n = the number of equiprobable stimuli, a = the basic motor speed component and b = the slope of the function relating RT to increases in complexity. If schizophrenics were differentially handicapped by task complexity, they should have shown either an exponential increase in RT as a function of the log of the number of stimulus, or a steeper linear slope as a function of log n. Venables, using two schizophrenic samples and a control group, found neither to be the case. The only significant difference was in variable "a". Schizophrenics were characterized by slower motor speed.

Process/reactive SZ: differences

Few published RT studies have made a distinction between process and reactive schizophrenics. Sutton & Zubin (1965) did not find significant differences between reactive and process schizophrenics in the RTs to identical, ipsimodal, and cross-modal stimuli, although reactives tended to be somewhat faster. Bellissimo & Steffy (1972) found that the process but not the reactive schizophrenics showed a significant crossover of regular and irregular PI series. There is no agreement as to whether regularity and irregularity of stimulus presentation affects process and reactive populations differentially in the RT task (Nuechterlein, 1977).

Zubin's theory

Shakow described the schizophrenic as one who is easily distracted from the purpose of the task, whereas Zubin portrayed him to be an individual unable to shift his focus easily. In the former, the emphasis seems to be upon lability of the attentional focus to the purpose of the task; in the latter, the emphasis is upon the rigidity of the focus extending from trial to trial. Zubin (1975) proposed a neural trace theory to account for cross-modal retardation. According to this theory, with the presentation of a stimulus, facilitatory and inhibitory traces remain within the organism's neuron pool, and have an effect on the processing of future stimuli. The processing of similar subsequent stimuli is facilitated, and the processing of dissimilar

subsequent stimuli is inhibited by these traces. Thus, a subject's RT will become faster (practice effect) with repeated presentations of the same stimulus since more facilitatory neuron traces will contribute to his response. Cross-modal retardation will also be more dramatic if several identical stimuli precede the cross-modal stimulus, since more inhibitory traces have accumulated. Zubin proposed that both facilitatory and inhibitory traces persist longer in the schizophrenic.

Mettler's neurological model of perceptual functioning in SZ

Mettler (1955) reported that cats with experimentally produced lesions of the striatum showed a characteristic incapacity to react appropriately to changing environmental events. He reported that attentional difficulty in SZ resulted from fluctuations in the vascular supply of the basal ganglia, causing the striatum to malfunction (Mannuzza, 1980).

Magnitude of difference hypothesis - Modality shift effect

Sutton et al (1978) mentioned that the "modality shift" effect distinguishes patients from controls. He thought that it had nothing to do with shifting attention across modalities. Rather, the magnitude of difference between the stimuli across modalities was greater than the magnitude of difference between the stimuli within modalities ("magnitude of difference" hypothesis).

The modality shift effect has been demonstrated in all types of schizophrenics (chronic and acute, process and reactive, drug-free and medicated) (Mannuzza, 1980).

Marcus (1973) found that children of schizophrenic mothers showed slow overall RT in comparison to normal control children. This suggests that the deficit is stable and not motivational (Mannuzza, 1980).

Nuechterlein & Dawson (1984) selected college students who had 2-7-8 profiles on the MMPI (a combination of elevated scales associated with schizotypal features), later schizophrenic diagnoses as well as affective psychoses. In comparison to a group of subjects with no elevated scales and a group with elevations on scales other than scale 8, the 2-7-8 subjects were found to detect fewer target stimuli and to have lower sensitivity on an adult version of CPT which again used a single digit target that was difficult to discriminate from non-target digits (Nuechterlein & Dawson, 1984).

Short-term recognition memory

Studies associated with short-term memory are usually divided into those using recognition measures and those using recall measures. Recent processing capacity theories have emphasized that recall requires more processing capacity.

Adolescents with a schizophrenic parent had lower overall sensitivity than children of normal parents in discriminating repeated items from new items. This difference was found to be attributable to their weaker initial short-term memory strength rather than to a greater loss of information from memory. Consistent with these results, researchers found that college students with 2-7-8 MMPI profiles had lower recognition memory strength than those without these profiles (Nuechterlein & Dawson, 1984).

Short-term recall memory

Studies found that children of schizophrenic mothers or fathers showed poorer immediate recall of letter sequences than children of normal parents in an Attention Span task. A second sample of 7- to 12-year-old children of schizophrenic parents was found to show similar poorer immediate recall for digit strings that were presented either aurally or visually in the Visual-Aural Digit Span test (Nuechterlein & Dawson, 1984). The evidence of impaired short-term recognition among children of schizophrenics and in college students with MMPI 2-7-8 profiles stresses deficits in recall but not recognition.

Koh et al (1973) found that schizophrenics showed poorer recognition for consonant-vowel-consonant nonsense syllables than normal subjects, but not for words. Deficient recognition memory in process SZ but not in reactive SZ caused poorer word recognition in the process group. These findings are explained by information input dysfunction rather than retrieval deficit (Nuechterlein & Dawson, 1984).

Concept formation

Another function carried out by short-term, working memory (WM) is the formation of concepts. In a study, subjects were asked to sort cards with varying numbers of irrelevant stimulus dimensions in a Concept Attainment task. The authors examined how many trials were necessary for the subject to identify the sorting principle. Children of schizophrenic mothers needed more trials than controls (Nuechterlein & Dawson, 1984).

Semantic memory and word production

Formal thought disorder (characteristic symptom in SZ) prompted investigations in the verbal associative network and speech production of samples at risk. It was reported that children of chronic schizophrenic mothers produced significantly more clang associations, chain associations and repetitions of the response words in a continuous association task (Nuechterlein & Dawson, 1984).

Studies of remitted, post-psychotic schizophrenics

Faulty information processing across premorbid, psychotic, and remitted post-psychotic SZ patients shows that the deficit is either a vulnerability indicator or a marker for SZ (Nuechterlein & Dawson, 1984).

Schwartz et al (1991) related RT variables to negative and positive symptoms.

Empirical work by Crow (1980) and Andreasen & Olsen (1982) linked negative symptoms to biological variables and cognitive deficits in SZ. Negative symptoms were not specific to SZ, occurring also in affective illness (Andreasen, 1987). Lack of specificity led to a distinction between the negative symptoms and the schizophrenic deficit state. The latter most probably is due to a deteriorating process, neurosphysiological in etiology. The deficit state was defined in two ways: by the persistence of negative symptoms and by the co-occurrence of negative symptoms with cognitive impairment, NSS and behavioral disorganization.

In their study, Schwartz et al (1991) included a measure of motor performance (finger tapping) to control for motor speed. They also included an experimental variation of the RT paradigm to increase the attentional demands of the task. They hypothesized that the association of negative symptoms and RT was specific to SZ, and that such specificity was not found with positive symptoms. The relationship of the deficit syndrome to RT performance was evaluated by including a measure of intelligence for cognitive impairment and a measure of neuropsychological performance. They also evaluated the attentional hypothesis in depression and after neuroleptics' use.

In the Schwartz et al (1991) study, 48 schizophrenic inpatients and 80 affective inpatients were used. The diagnosis was based on a semi-structured interview and research diagnostic criteria (RDC) (Spitzer et al, 1981). The negative symptoms were rated with Andreasen's scale (1986),

using the sum of the global ratings from five subscales. The sum of the alogia and flat affect scales was also abstracted, based on Crow's (1985) report that the full scale was likely to be confounded by depression and psychoticism. Thus, the Brief Psychiatric Rating Scale was used to measure depression and psychoticism (psychoticism is the sum of thought disturbance and paranoid factors). Two other features of the deficit syndrome were evaluated (intelligence and neuropsychological deficits). They were compared with negative symptoms. Intelligence was tested using the Full Range Picture Vocabulary Test. Neuropsychological performance was measured on a 19-item battery (Luria, 1966), and included tests of motor, somatosensory, language, visual-spatial, and memory functions. Visual RT was measured in msecs with automated equipment. Two conditions were employed: simple RT (designated RT1), and RT while subjects counted out loud by twos (designated RT2). Two motor tests (finger tapping and the Purdue pegboard) were included to form a contrast with the RT conditions. Tapping speed was measured electronically. Finger tapping also evaluated the relationship between RT and negative symptoms**.**

In the study of Schwartz et al (1991) two patterns emerged: (1) The deficit triad of negative symptoms, intelligence and neuropsychological deficits was significantly interrelated in the schizophrenic group but not in the affective group, (2) The absolute correlations between negative symptoms and depression, positive symptoms, and neuroleptics were all reduced in the schizophrenic sample when the abbreviated version of Andreasen's scale was used. Negative symptoms were associated with the RT variables and finger tapping in the schizophrenics. These were nonsignificant in the affective group. Thus, schizophrenics with high levels of negative symptoms were more likely to have slower RT's, be more variable, and tap at a slower rate. Positive symptoms in the schizophrenics had an adverse effect on the RT2 condition (both in latency and variability). The association of negative symptoms and RT was not increased in the divided attention condition (RT2). No relationship between neuroleptics and negative symptoms emerged in this study (Schwartz et al, 1991).

As already mentioned, with the use of the full Andreasen scale, two interactions were significant (RT2 latency and variability). With the abbreviated Andreasen scale, all RT variables were significant. These results demonstrated that the association of negative symptoms and RT

was specific to the schizophrenic group. Schizophrenics with few negative symptoms performed at the level of non-psychotic affective disorders. Schizophrenics with many negative symptoms performed at the level of undifferentiated schizophrenics. Negative symptoms correlated with slowing and variability specific to SZ.

Negative symptoms though are only one component of the deficit syndrome. The deficit syndrome also includes cognitive impairment and neuropsychological dysfunction. Neither intelligence nor neuropsychological performance, however, was specifically associated with the RT variables in the schizophrenic group in the Schwartz et al (1991) study. There was no association between negative symptoms and laboratory measures of attention.

Schwartz et al (1991) also found that controlling for motor speed did not influence the specific association of RT and negative symptoms in the schizophrenic group.

Such findings favor the attentional hypothesis, as RT is a simple sensorimotor task without a significant cognitive or perceptual component. The association of RT and negative symptoms in the schizophrenics was of the same magnitude in the RT1 and the RT2 condition. A divided attention task they used, however, was associated with psychoticism (Schwartz et al, 1991).

Schwartz et al (1989) also studied a young chronic group of schizophrenics and a group of affectives for simple RT and RT while they engaged in a concurrent task. The affectives were subdivided by the presence of psychotic features. The results showed that extreme slowing of RT was due to psychoticism and was not characteristic of nonpsychotic affective illness. Extreme intra-individual variability (IIV), however, was specific to SZ. They thought that it was a trait marker of the disorder.

In approximately 50 studies, schizophrenics were found to be slower and more variable than normal controls. RT appeared to be stable over time, to be slowed in remitted patients and to be also predictive of the outcome. RT was independent of the patient's clinical state (Schwartz et al, 1989). Slowing of RT, however, was not specific to SZ since it was also found in depression (Schwartz et al, 1989). Thus, RT slowing appears to be due to psychoticism, as it is found to the same extent in schizophrenics and in affectives with psychotic features. Time sharing, (which loads capacity and slows RT), appears to be most detrimental to psychotic patients. The extreme IIV, however, appears to be specific to SZ, as it is independent of psychoticism, and so

may be a trait marker of this disorder (Schwartz et al, 1989). IIV of RTs can estimate the stability of information processing, which is core disturbance of SZ.

The purpose of the Rentrop et al (2010) study was to assess IIV in high-functioning patients with SZ and relatively preserved cognitive performance (Rentrop et al, 2010). IIV is an easily obtained measure and highly sensitive to cognitive deficits. IIV is not easily visible in a high-functioning patient group. With slower RTs though, it reflects a core deficit in the stability of information processing. There is also a relationship with work capability. Therefore, the authors thought that the investigation of IIV was a clinical measure of the ability to work (Rentrop et al 2010).

In the Rentrop (2010) study, 28 high-functioning patients with SZ and 28 controls performed a Go/Nogo task and a CPT. IIV differentiated consistently between groups. An Ex-Gaussian distribution revealed that patients had a higher proportion of slow responses reflected by an increased tau parameter. The tau parameter was correlated with work capability in the sample with SZ. The increase in variability was mainly caused by a positively skewed distribution with a higher proportion of long RTs (Rentrop et al, 2010). The Ex-Gaussian distributional model provided quantitative measures of the distributional properties of RTs for each individual. The important role for IIV as a direct measure of cognitive consistency in a working context was established.

The study of Rentrop et al (2010) aimed to answer if schizophrenics with relatively preserved cognitive test performance showed increased IIV of RTs. The authors reported three major findings: First, that IIV showed significant differences at the group level between schizophrenics and controls even though other measures of cognitive functioning were similar. Second, that increased IIV of the group with SZ was due to a higher proportion of slow responses reflected by the exponential part of an Ex-Gaussian distribution. Third, that the exponential part was linked to a measure of work capability.

In this study, the authors made a comparison with Attention Deficit Hyperactivity Disorder (ADHD). They attempted this because SZ and ADHD share similar biochemical background. First, a reduction in prefrontal DA transmission which occurs in both SZ and ADHD can lead to reduced activity at prefrontal D1 receptors which is the main mechanism underlying increase in

cortical noise (Rentrop et al, 2010). Second, because cerebellar dysfunction is a key feature of cognitive dysmetria and has also been observed in both disorders (in structural as well as functional neuroimaging studies). Third, because increased IIV in SZ has also been found on an eye blink conditioning task, which relies on the integrity of the cerebellum and not the prefrontal cortex (Rentrop et al, 2010). Thus, they thought that increased IIV could be due to comparable disturbances in fronto-cerebellar circuits in SZ and ADHD (after all, both disorders have attentional, executive and motor dysfunctions).

The study of Rentrop et al (2010) on IIV in SZ is not the only one. There are other studies on RT variability in SZ as well. For example, Karantinos et al (2014) studied a group of 23 patients suffering from DSM-IV SZ and a group of 23 age-matched control subjects who performed two RT tasks requiring basic sensorimotor processing engaging two different motor systems: the Finger Lift Reaction Time task and the Voluntary Saccade RT task. The Ex-Gaussian model was also applied to the RT distributions measuring the mean (mu), and standard deviation (sigma) of a Gaussian component thought to reflect sensorimotor processing and an exponential component (tau), thought to reflect an intermediate decision process. In both tasks, a significantly larger RT IIV separated patients from controls. The RT IIV in the two tasks was highly correlated only for patients. Both sigma and tau were significantly higher in the patient group with tau being the best predictor of SZ. Only in the patient group were sigma and tau highly correlated between the two tasks.

The results of the Karantinos (2014) study reflect a deficit in information processing apparently not confined to decision processes related to the frontal cortex. They indicate dysfunction in distributed neural networks which modulate adaptive regulation of performance.

There is no doubt that several groups have suggested that RT IIV is a specific characteristic of cognitive and sensorimotor processing stability (Rentrop et al, 2010). Neuroimaging supported this, since it showed a positive correlation between RT IIV and activation of the frontal regions such as the dorsolateral prefrontal cortex (DLPFC) (Karantinos et al 2014). Also, in a simple visuomotor RT task, RT IIV was predicted by the rate of increase in pre-MEG activity recorded from left central-frontal areas (Smyrnis et al, 2012). In a simple manual response task mean RT was larger for all groups with psychotic symptoms (both SZ and affective disorder). But the

highest RT IIV was found in schizophrenics (Schwartz et al, 1989). Kaiser et al (2008) also compared RT IIV in a go/no-go task among groups of patients with SZ, major depression and borderline personality disorder. The RT IIV clearly dissociated SZ patients from all other groups. RT variability was consistently found highest in schizophrenics.

Saccadic RT and variability in schizophrenics

RT is regularly measured in the study of saccadic eye movements, which are widely used in the study of psychiatric disorders and especially SZ (Karantinos et al 2014). In a review of studies of visually guided saccades in SZ, Gale and Holzman (2000) concluded that the mean RT in patients did not differ from that of controls. In a recent study of visually guided saccades, RT IIV but not mean saccadic RT was increased in patients with SZ compared to controls (Smyrnis et al, 2009). Based on the similarity of RT results of SZ patients performing manual and saccadic tasks, Smyrnis et al (2009) hypothesized that RT distribution characteristics could provide a robust dissociation of patients with SZ from healthy controls in both types of sensorimotor processing. The authors hypothesized that the increase in RT variability in SZ would be the same for the oculomotor and the hand motor system. Such a finding reflects a common mechanism which produces increased variability in different brain systems (Smyrnis et al, 2009).

In the Karatinos et al (2014) study all RT distribution descriptive measures were significantly different for patients compared to controls (Table 4.1 Column G). The patients displayed longer mean RTs, larger variance of RTs and more skewed RT distributions compared to controls (fig. 4.1).

The number of late responses was very small for both tasks and groups. Patients though had significantly more late responses than controls. RT distribution descriptive measures for each subject were similar in both tasks as indicated by no significant effect of task within subjects (Table 4.1 column T).

A significant interaction effect of group and task for both mean RT and SD of RT was due to a larger increase in both for patients in the voluntary saccade task compared to the finger lift task (Table 4.1 column G×T).

Level of education and laterality had no significant effect on RT distribution descriptive measures (Karantinos et al, 2014).

Table 4.1 Repeated measures ANCOVA analyses of RT distribution statistics

	Finger lift task controls	Finger lift task patients	Voluntary saccade task controls	Voluntary saccade task patients	G $F_{1,43}$	T$F_{1,43}$	G×T$F_{1,43}$
RT distribution descriptive measures							
Mean (ms)	202 (20)	239 (31)	226 (45)	305.9 (82)	**18.3****	0.01	**8.02**
Standard deviation (ms)	43 (12)	74 (18)	60 (19)	106.6 (39)	**39.3****	0.006	**5.37**
Coefficient of variation	0.21 (0.05)	0.3 (0.06)	0.27 (0.07)	0.35 (0.08)	**30.8****	0.13	0.2
Skewness	4.75 (2.36)	3.1 (1.23)	3.41 (2.07)	2.20 (1.1)	**8.13***	0.05	0.07
Number of late responses	1.1 (1.35)	3.0 (4.31)	3.0 (3.08)	9.1 (10.17)	**7.56***	0.55	2.31
Ex-Gaussian model parameters							
Mu (ms)	174 (16)	181 (24)	178 (35)	213 (61)	3.63	0.53	2.96
Sigma(ms)	15 (5)	22 (10)	16 (6)	34 (25)	**8.7***	0.67	2.88
Tau (ms)	27.9 (9)	58.4 (18)	48.3 (20)	93 (43)	**34.8****	1.104	**6.89**

The table presents the result for the repeated measures ANCOVAs performed on the RT distribution statistics from both the finger lift and voluntary saccade tasks for patients and controls. G: between subject group main effect (controls/patients), T: within subject task main effect (Finger Lift RT task/Voluntary Saccade RT task), G×T: group by task interaction effect. SD of mean values are presented in parentheses. Bold *F* values indicate statistical significance: no asterisk, $P<0.05$,$^{*}P<0.01$, $^{**}P<0.001$ (Karantinos et al, 2014)

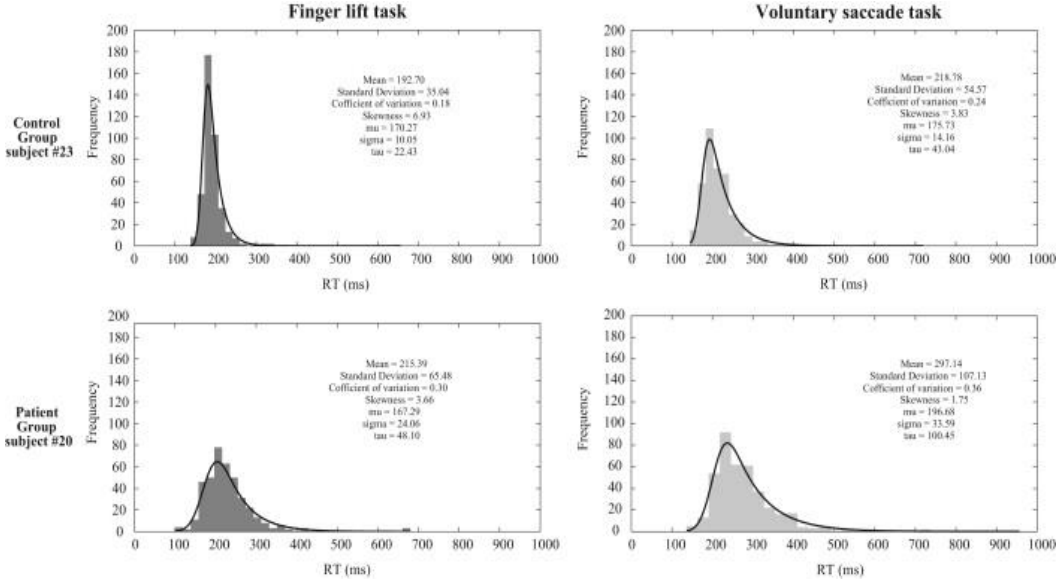


Fig. 4.1. The plots in the upper raw of this figure show the RT distributions for a representative control subject (subject no 23) and those in the lower raw of this figure show the RT distributions for a representative patient with schizophrenia (patient no 20) in the finger lift task (left, finger lift) and the volitional saccade task (right, voluntary saccade). The frequency of RT is plotted in the *y*-axis and the RTs are plotted on the*x*-axis (in ms). The Ex-Gaussian model fit on the RT distribution is also plotted (solid black line). The descriptive measures as well as the Ex-Gaussian model measures are shown in each plot (Karantinos et al, 2014)

In the study of Karantinos et al (2014), the model that best discriminated patients from controls based on RT was the finger lift task which contained two predictors, RT SD (F=48.57, P<0.001) and RT skewness (F=9.82, P<0.003). This accurately identified 91.3% of the control subjects and 82.6% of the patients. The model that best discriminated patients from controls based on RT in the voluntary saccade task contained only a single predictor, the SD of RT (F=26.63, P<0.001). This accurately identified 91.3% of controls and 73.9% of patients. Combining finger lift and voluntary saccade task measures resulted in the same discriminant model as produced from the finger lift task alone with SD and skewness of RT distribution as the significant predictors (Karantinos et al, 2014).

The model that best discriminated patients from controls using RT in either the finger lift or the voluntary saccade task included only tau as a significant predictor (F=54.69, P<0.001, F=10.6, P<0.01, respectively). The finger lift discriminant model correctly identified 95.6% of control subjects and 86.9% of patients whereas the voluntary saccade discriminant model correctly identified 91.3% of control subjects and 60.9% of patients. Combining Ex-Gaussian model parameters from both finger lift and voluntary saccade tasks resulted in the same discriminant model produced by data from the finger lift task with tau of the finger lift task as the only significant predictor (Karantinos et al, 2014).

Table 4.2 Pearson correlations between finger lift and voluntary saccade task parameters.

	Controls	Patients
RT distribution descriptive measures		
Mean	**0.56***	**0.64***
Standard deviation	0.17	**0.64***
Coefficient of variation	−0.01	0.38
Skewness	10.28	0.32
Number of late responses	0.06	−0.06
Ex-Gaussian model parameters		
Mu	**0.43**	0.32
Sigma	0.10	**0.65****
Tau	0.36	**0.56***

The Pearson correlation coefficients marked by bold indicate P<0.05., P<0.01, P<0.001.
The table presents the Pearson correlation coefficients comparing RT distribution statistics between the two tasks for each subject group separately (Karantinos et al, 2014)

In healthy controls, only mu (the Ex-Gaussian RT mean) was significantly correlated between the finger lift and voluntary saccade task. In contrast, in the patient group, sigma (Ex-Gaussian SD) and tau (exponential component) were significantly correlated between tasks whereas mu (Ex-Gaussian mean) was not (Table 4.2). None of the RT distribution statistics was significantly correlated with the dose of the antipsychotics in the patient group.

The RT distribution of schizophrenics who performed two volitional visuo-motor tasks was significantly different from that of controls. The patient group exhibited larger RT mean, SD, CV and skewness. Patients also produced significantly more late responses. The increase of the late responses in the finger lift task of patients with SZ indicates possible lapses of attention. Increases in RT distribution in SZ patients who performed the finger lift task have been observed in a number of previous studies measuring RT of manual responses. Thus, there is no doubt that many studies in the past suspected the increase in the IIV to be due to disturbance of attention in SZ (Kaiser et al, 2008, Rentrop et al, 2010).

The main difference between Karantinos et al (2014) study and the others was the minimum cognitive demand in order to focus on the most elementary sensorimotor processes related to volition. RT distribution differences between patients and controls in this very simple task were robust and easily observed at the individual subject level. This identified the increased RT variance as the most significant measure dissociating normal individuals from patients with SZ. As seen from Fig. 4.1, patients produced not only more late responses but also more early responses than controls. It is the shape of the distribution that dissociates the two groups.

The study of Karantinos et al (2014) extended the finding of increased RT IIV measures in SZ reported by other studies (Kaiser et al, 2008, Rentrop et al, 2010) because it showed the same increase in a different motor system, the saccadic eye movement system. The main predictor of schizophrenics versus controls was the RT IIV. The dissociation between schizophrenics and controls showed that increased RT IIV was a measurement of specific information processing deviance in schizophrenics (Karantinos et al, 2014).

The adaptive gain theory proposes that locus coeruleus (LC) noradrenergic neurons exhibit two modes of activity, phasic and tonic (Karantinos et al, 2014). Phasic LC activation facilitates decision-making (DM) and thus optimizes performance of a specific task. Phasic LC signals reach

motor areas such as the primary motor cortex. They facilitate motor response based on previous decisions. In accordance with the adaptive gain LC theory, it was observed that when normal individuals received an a1-adrenergic antagonist, their performance in RT tasks became more variable. This was reversed by an a1-adrenergic agonist (Karantinos et al, 2014). This appears a convincing model of how the basic LC-driven attentional modulation drives decision and volitional control (Karantinos et al, 2014).

But also, as already mentioned, SZ has been linked to orbitofrontal cortical dysfunction as well as to functional and anatomical abnormalities of the anterior cingulated cortex. These areas are connected to the dopaminergic reward system of the brain. The high IIV observed in Karantinos et al (2014) study in two volitional movement tasks independent of motor output reflects a deviance in information processing due to dysfunction in neural networks involving both noradrenergic and dopaminergic brain systems which control and regulate adaptive regulation of performance.

Cognitive and IQ studies

Studies report poor performance in psychotic patients on tasks testing a range of cognitive functions. Current IQ is often not matched between groups and it is difficult to determine whether this is a generalized deficit or a specific abnormality.

In a study (Leeson et al, 2010), 53 first-episode psychosis patients and 53 healthy controls, matched for sex, age, and full-scale IQ, were compared on Wechsler Adult Intelligence Scale (WAIS) subtests which represented perceptual organization, verbal comprehension, processing speed, working memory (WM) as well as tests of executive function and episodic memory.

The groups showed similar performance on all WAIS subtests except digit symbol processing speed, on which the patients were significantly worse. Patients were also worse on measures where performance correlated with digit symbol score, namely working and verbal memory tasks. Standardized residual scores for each subtest were calculated for each patient using the difference between their actual subtest score and a predicted subtest score based on their full-scale IQ and the performance of controls (table 4.3). Scaled scores and residual scores were examined for relationships with clinical measures (Leeson et al, 2010).

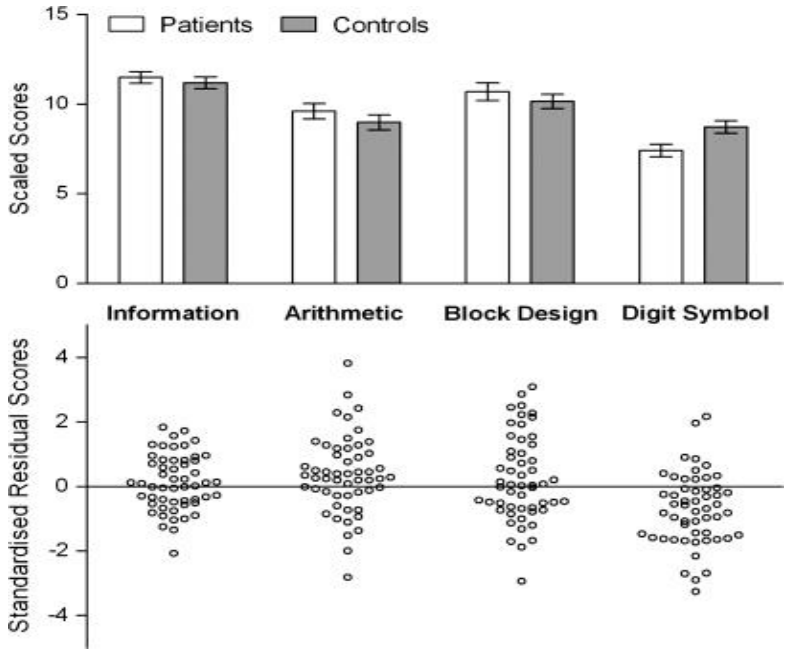
Table 4.3. Comparison of SZ and control groups on demographic details, executive function, and memory

	Patients	Controls	Comparison
N	53	53	
Sex	34 M/19 F	34 M/19 F	
Age in years: mean (SD)	26.77 (7.75)	26.49 (6.70)	$F_{1,105} = 0.04$, $P = .841$
Years of education: mean (SD)	12.79 (2.07)	13.74 (2.14)	$F_{1,105} = 5.32$, $P = .023$
Cognitive measures: mean (SD)			
Premorbid IQ (WTAR)	101.30 (9.27)	97.75 (8.91)	$F_{1,105} = 4.04$, $P = .047$
Current IQ	98.67 (13.68)	98.32 (13.65)	$F_{1,105} = 0.02$, $P = .893$
Spatial Span	5.84 (1.19)	6.37 (1.33)	$F_{1,103} = 4.39$, $P = .039$
Spatial Working Memory (errors)	13.51 (9.80)	8.90 (8,84)	$F_{1,103} = 14.47$, $P < .001$[a]
Tower of London (perfect solutions)	7.49 (2.69)	8.42 (1.91)	$F_{1,101} = 3.13$, $P = .08$
IDED (extradimensional shift errors)	13.51 (9.80)	8.90 (8.83)	$F_{1,101} = 6.22$, $P = .014$
Verbal memory (summed recall over learning trials)	42.98 (8.32)	48.71 (10.25)	$F_{1,105} = 10.00$, $P = .002$[a]
Pattern Recognition Memory (number correctly recognized)	19.73 (3.05)	21.44 (2.45)	$F_{1,103} = 9.97$, $P = .002$[a]

- *Note*: M, male; F, female; WTAR, Wechsler Test of Adult Reading; IDED, Intra/Extra Dimensional Set Shift.
- [a] Significant after Bonferroni correction ($P < .005$) (Leeson et al, 2010).

Clinical and neuropsychological assessments

In the study of Leeson et al (2010) psychotic symptoms were assessed with the Scales for the Assessment of Positive and Negative Symptoms. Scores for the 3 symptom-derived syndromes (positive, negative, disorganization) were calculated for each patient. The Hamilton Rating Scale for Depression and The Young Mania Scale were used to assess affective symptoms. To establish the timing of onset of the psychotic illness, the Nottingham Onset Scale (NOS) was used. Current IQ was measured using a short form of the WAIS-III validated for use with SZ [information (verbal comprehension index), arithmetic (WM index), block design (perceptual organization index), and digit symbol (processing speed index)]. A prorated full-scale IQ (FSIQ) was calculated using these 4 subtests, Premorbid IQ was estimated using the Wechsler Test of Adult Reading (WTAR). Memory and executive function tests were taken from the Cambridge Automated Neuropsychological Test Battery. Verbal learning and memory were measured with the Rey Auditory Verbal Learning Task (Table 4.4, fig 4.2, Leeson et al, 2010).



- Fig 4.2 Scaled scores and standardized residual scores for each Wechsler Adult Intelligence Scale III Subtests. Mean patient and control data are shown for scaled scores and individual patient data are shown for the residual scores (Leeson et al, 2010)

Table 4.4 Correlations between IQ and WAIS subtest–scaled scores and other neuropsychological measures in patients and controls

	Controls					**Patients**				
	FSIQ	Information	Arithmetic	Block Design	Digit Symbol	FSIQ	Information	Arithmetic	Block Design	Digit Symbol
Spatial Span	0.28*	0.13	0.32*	0.09	0.23	**0.44****	0.30*	0.27	0.33*	0.30*
Spatial Working Memory (errors)	**0.46****	0.26	**0.44*****	0.38**	0.26	**0.53*****	0.37**	0.42**	0.25	**0.50*****
IDED (extradimensional shift errors)	**0.45*****	0.30*	0.38**	**0.48*****	0.13	0.40**	0.29*	0.31*	0.38**	0.12
Verbal learning (summed recall over learning trials)	**0.47*****	0.38**	0.32*	0.25	**0.43*****	0.31*	0.13	0.05	0.20	**0.55*****
Pattern Recognition Memory (number correctly recalled)	0.28*	0.27	0.12	0.17	0.27	0.37**	0.29*	0.38**	0.17	0.21

- *Note:* WAIS, Wechsler Adult Intelligence Scale; FSIQ, full-scale IQ. Emboldened figures are significant after Bonferroni correction ($P < .002$). *Significant at $P < .05$; **significant at $P < .01$; ***significant at $P < .001$. (Leeson, 2010).

IQ, memory, executive function, and processing speed in recent onset psychosis

Leeson's et al (2010) study aimed to investigate whether performance on a test of processing speed, digit symbol coding, was disproportionally impaired in patients with recent-onset SZ who had intact intellectual function. It also examined the relationship between processing speed, memory and executive function as well as symptoms at first episode and over time. As it has already been mentioned, the authors found that the patients were significantly impaired on digit symbol coding but they were no different from controls on information, arithmetic, or block design. Digit symbol coding was by far the most sensitive marker of cognitive impairment in SZ. The authors also showed that digit symbol impairment was the most sensitive indicator of cognitive impairment in nonpsychotic relatives of schizophrenics. These findings indicate that impaired digit symbol performance is a stable trait in SZ and reflects an abnormal cognitive process central to the disorder. It is present at the onset of psychosis with intact performance on other tests of general intellectual ability.

Digit symbol performance was also sensitive to symptom severity in this study. Following correction for multiple comparisons, only an inverse relationship between the negative syndrome and digit symbol-scaled score remained significant. When the authors examined the predictive value of digit symbol performance in a subset of patients, the magnitude of relative impairment in digit symbol performance at the first psychotic episode was a prognostic factor for poor outcome and development or persistence of negative symptoms (Leeson et al, 2010). In this study, despite matching for IQ, patients were impaired on memory and executive function. The differences were particularly large for verbal learning, visual recognition memory, and spatial WM manipulation. Verbal learning and spatial WM correlated strongly with digit symbol performance in the patients and to a lesser extent in controls. This research indicates that digit symbol is primarily a test of speed, particularly cognitive speed, in healthy controls (Leeson et al, 2010).

Yarkoni et al (2009) investigated whether there are brain regions that show a general relationship between trial-by-trial RT variability and activation across a range of cognitive tasks. The relation between trial-by-trial differences in RT and brain activation was modeled in five different fMRI datasets spanning a range of experimental tasks and stimulus modalities. Three

main findings were identified. First, in many gray and white matter regions, activation was delayed on trials with long RTs relative to short RTs. This finding suggested delayed initiation of underlying physiological processes. Second, in lateral and medial frontal regions, activation showed a “time-on-task” effect which increased linearly as a function of RT. RT variability reliably modulated the BOLD signal not only in the gray matter but also in diffuse regions of the white matter. The results highlighted the importance of modeling trial-by-trial RT in fMRI analyses. They also showed that RT variability could investigate the white matter BOLD signal (Yarkoni et al (2009).

There are several reasons to predict the existence of task-independent relations between activation and RT. First, many cognitive processes are expected to be time-locked to participants' overt responses (start of motor response, processing of tactile or visual feedback). Also, the temporal onset of the hemodynamic response (HDR) should vary as a function of RT in sensorimotor brain regions. Thus, when participants respond more slowly, activation should initiate later than when participants respond quickly. Any variation in either the amplitude or the duration of neurocognitive processes might be expected to reliably modulate RT. In cases where short-RT and long-RT trials are differentiated only by the duration over which some neurocognitive process unfolds, (with no difference in amplitude), linear summation predicts that the BOLD response will attain a larger amplitude for trials with longer RTs. Any trial-by-trial differences in RT will be associated with changes in the amplitude or intensity of some cognitive processes. As the cognitive resources allocated to a trial increase, the amplitude of activation in brain regions that support those resources will increase while RTs will decrease (Fig 4.3 C). This predicts that there must be a negative correlation between RT and the BOLD response in regions associated with task-related resources.

It was found that decreased activation in fronto-parietal regions just prior to trial onset was associated with longer RTs. The researchers attributed this to momentary lapses of attention. These possibilities (a temporal shift, a positive correlation with duration, and a negative correlation with amplitude) are not exhaustive, nor are they mutually exclusive. To the contrary, it is likely that RTs on most trials reflect a mix of influences, resulting in complex response shapes.

Fig.4.3 D illustrates the hypothetical response for two trials that differ in their onset, amplitude and duration. The presence of multiple influences could make RT-related activation difficult to detect if general trade-offs exist. If an increase in amplitude is precisely offset by a decrease in duration, it will be difficult to detect a difference in the resulting HDRs at short durations. Some influences might be stronger than others.

To test for the presence of systematic relations between RT and brain activation, Weissman et al (2006) assessed the relationship between trial-by-trial variation in RT and brain activation at a relatively broad, task-independent level. Data from five different fMRI experiments were reanalyzed, with datasets chosen to span a range of experimental tasks (WM, episodic memory, decision-making, and affective rating tasks), fMRI designs (event-related and mixed blocked/event-related), and stimulus modalities (words, affective pictures, faces, and numbers).

The authors searched for regions with consistent relationship across studies between BOLD activation and RT. Results provided strong evidence for two of the three patterns predicted above. Specifically, they identified (a) temporal shifts in the onset of the BOLD response on trials with longer RTs throughout much of the brain, and (b) positive correlations between RT and activation in a number of frontal, parietal, and thalamic regions. They also identified consistent relations between trial-by-trial changes in RT and activation strength in white matter regions. They provided evidence that BOLD signal in white matter can be detected (Weissman et al, 2006).

RT-related activation in gray and white matter regions

The Yarkoni et al (2009) studies in activated regions of gray matter included large bilateral foci in medial frontal cortex, frontal operculum, lateral PFC, anterior PFC, visual cortex, medial cerebellum, and thalamus, as well as lateralized and/or more circumscribed foci in the precuneus, posterior cingulate cortex, and inferior parietal cortex (fig 4.4, fig 4.5).

In addition to the activations in cortical and subcortical gray matter regions, there were activations in regions located within white matter. RT-related activation was identified in the right lateral genu of the corpus callosum and in parts of the posterior corona radiata bilaterally. This was surprising since BOLD signal in white matter is weaker than in gray matter. The BOLD

signal weakness in the white matter is due to the lower metabolic activity of white matter (fig 4.6, fig 4.7).

RT-related and task-related activation

In Yarkoni et al (2009) study, for each ROI that showed an effect of RT, the authors estimated and plotted the corresponding task-related responses and applied the same linear contrasts testing for shift versus amplitude differences (Fig. 4.3 C, D). Task-related responses differed qualitatively from RT-related responses in both gray and white matter ROIs. In gray matter ROIs, task-related changes in the amplitude of activation were generally stronger than corresponding RT-related effects. That is, z-scores for the amplitude contrast were consistently larger for task-related effects than for RT-related effects (despite the fact that it was the RT effect that was used to define the ROIs in the first place).

In contrast, in white matter ROIs, a striking discrepancy was observed between RT-related and task-related responses. Task-related responses were much less reliable than RT-related responses. They showed little consistency across studies and failed to resemble a canonical HRF (Fig 4.6, 4.7). This suggested that it was the RT-related modulation of the BOLD signal in white matter that was strong enough to be reliably detected (Yarkoni et al, 2009).

The contribution of Yarkoni et al (2009) was the identification of gray and white matter brain regions in which activation correlated with trial-by-trial differences in RT across a broad range of tasks. Evidence was found for both temporal shifts in RT-related activation. Delayed onset of cognitive processing, and uniform positive correlations between RT and activation in frontal regions, reflected a “time-on-task” effect of sustained attention. It was evident that there is a reliable effect of RT on BOLD signal in white matter.

What Yarkoni et al (2009) initially suggested was that the influence of task general preparatory or alertness-related processes on RT was negligible in comparison to the dominant time-on-task effect. But the results of Yarkoni et al (2009) argued against such an interpretation, because (a) in frontal regions associated with cognitive control, the late positive correlations with RT were substantially larger than the early negative correlations, and (b) an early dip in activation was observed in all regions, including sensorimotor regions that are unlikely to play a role in asserting control.

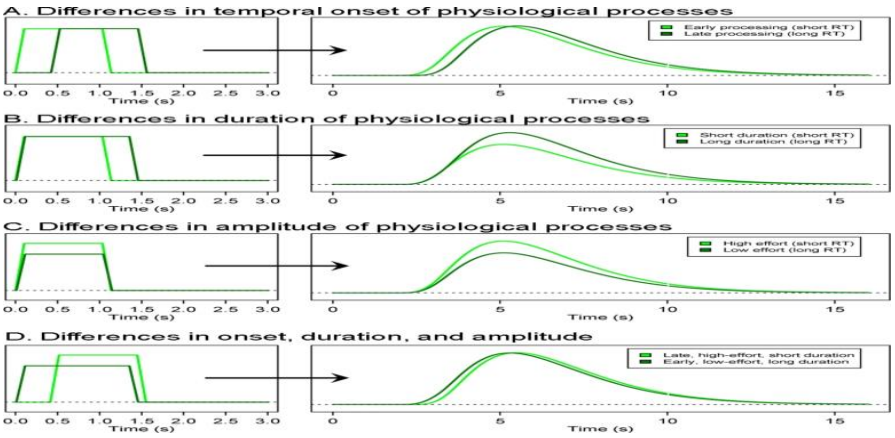


Fig 4.3 Hypothetical effects of changes in RT-related physiological processes on the BOLD response. (A) changes in onset. (B) changes in duration. (C) changes in amplitude (Yarkoni et al, 2009)

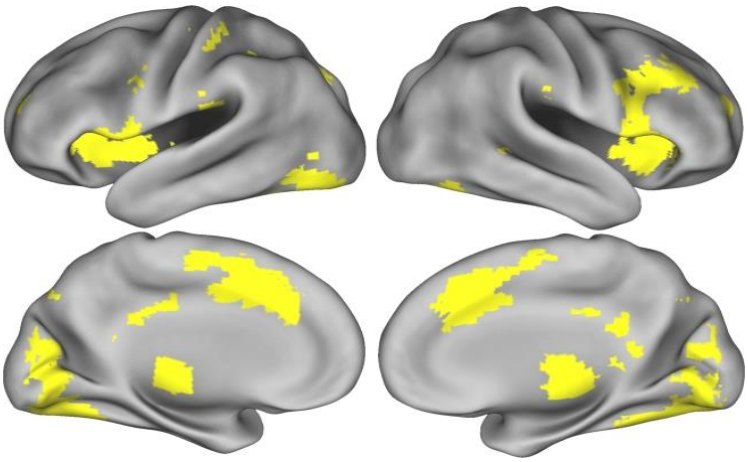


Fig 4.4 Cortical regions that showed significant RT-related activation in all five samples. Clockwise from top left ,left lateral, right lateral, left medial, and right medial views of the cortical surface (Yarkoni et al, 2009)

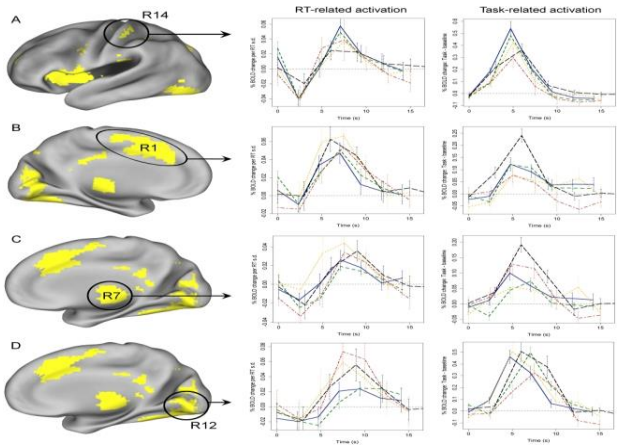


Fig 4.5 Time courses of RT-related activation in representative gray matter ROIs. Each line represents activation in a different sample. Left time course column: RT-related activation; right time course column: general task-related activation (i.e., task vs. baseline. Error bars reflect 95% confidence intervals (C.I.) (Yarkoni et al, 2009)

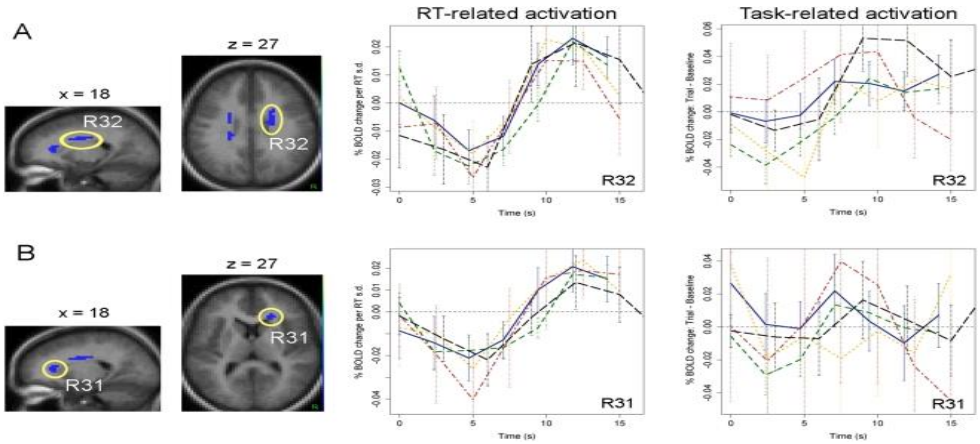


Fig 4.6 Time courses of RT-related activation in representative white matter ROIs (Yarkoni et al, 2009)

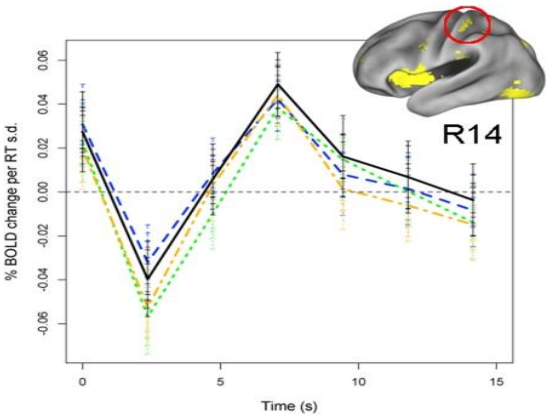


Fig 4.7. 1. RT-related activation in somatosensory cortex estimated separately by trial type in Sample 2. Each colored line represents the time course of RT-related activation estimated for a different trial type, after controlling for a range of experimental covariates. The black line represents the original estimate when collapsing across all trial types. Error bars indicate 95% C.I. (Yarkoni et al, 2009)

An unexpected finding of Yarkoni's et al (2009) study was the presence of a consistent association between trial-by-trial RT variability and BOLD signal in white matter regions. The white matter response appeared to have the same fundamental characteristics as the gray matter response, but evolved much more slowly. Increases in white matter activation might be associated with shorter RTs because they serve some functional purpose. They may facilitate more rapid communication between different gray matter regions on trials with short RTs. Another interesting study is the study of Ngan & Liddle (2000) which used simple RT, choice RT and Stroop tasks to explore the relationship between RT and symptom profiles in patients with fluctuating illness (*n*=24), persistent illness (*n*=17) and normal controls (*n*=16). The authors tested the hypothesis that in patients with persistent illness, psychomotor poverty was associated with impaired initiation of activity, and that disorganization was associated with

impaired selection in both persistent and fluctuating illness. Generally, in the simple RT task, patients with persistent illness performed worse than patients with fluctuating illness and controls. Both patient groups performed worse than controls in the choice RT tasks. Psychomotor poverty was found to be associated with simple RT in patients with persistent symptoms. Disorganization was associated with poorer performance on the choice RT task in both patient groups (Ngan & Liddle, 2000).

In the Ngan & Liddle (2000) study, 41 patients satisfying DSM-IV criteria for SZ were studied. All patients were receiving antipsychotics. Sixteen controls (with no DSM-IV axis one diagnosis) were also included. Symptom severity was rated using the Scale for Assessment of Positive Symptoms (SAPS) and the Scale for Assessment of Negative Symptoms (SANS) (Andreasen, 1990). Movement side effects were rated using the Simpson–Angus scale for Parkinsonism, Abnormal Involuntary Movement scale, and the Barnes Akathisia scale. Syndrome scores were calculated from the SANS and SAPS item as follows: reality distortion=global hallucination score+global delusion score; disorganization syndrome=inappropriate affect+positive formal thought disorder+poverty of content of speech; negative symptoms=sum of the global scores for alogia, asociality, affective flattening and avolition. The chronicity of illness was established using Global Assessment of Function (GAF) ratings for the best level of functioning during the previous 1 year and previous 5 years.

The patients were divided into two groups based on highest level of functioning in the previous year. Patients who had best GAF score in the previous year less than 50 were classified as having persistent illness. Patients with a previous year's best GAF score of 50 or higher were classified as having fluctuating illness. The results suggested that persistent illness, negative symptoms, and impaired initiation reflected dysfunction associated with chronic structural abnormalities. As for impaired selection processes and disorganization, data indicated that they occur in both persistent and fluctuating illness.

The table 4.5 presents significant correlations between clinical syndromes and RT tasks by group. Slower RT in the simple RT tasks was associated with negative symptoms and with disorganization in patients with persistent illness but not in patients with fluctuating illness. Slower RT in the forced RT task was related to disorganization in both persistent and fluctuating

illness groups. No other correlations between symptom profiles and RT reached statistical significance (Ngan & Liddle, 2000).

Table 4.5 Correlations of reaction time with symptoms[a]

	Persistent illness				Fluctuating illness			
	Simple reaction time		Forced choice reaction time		Simple reaction time		Forced choice reaction time	
Symptom	***r***	***P***	***r***	***P***	***r***	***P***	***r***	***P***
Negative symptoms	**0.547**	**0.023**	0.352	0.166	0.202	0.345	0.120	0.575
Disorganization	**0.564**	**0.018**	**0.550**	**0.022**	0.266	0.208	**0.424**	**0.039**
Reality distortion	0.096	0.713	0.147	0.574	−0.181	0.398	−0.097	0.651

aNo significant correlations between symptoms, self-generated choice reaction time and Stroop tasks (Ngan & Liddle, 2000).

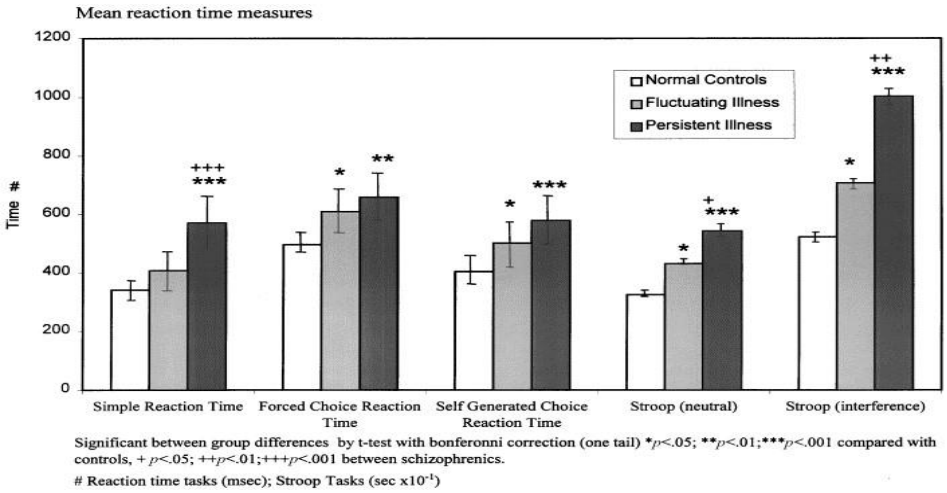


Fig.4.8 Reaction time differences (Ngan & Liddle, 2000)

In all five cognitive tasks used in this study, the patients with persistent illness performed worse than the patients with fluctuating illness. Patients with fluctuating illness performed worse than the normal controls. The analysis of the magnitude of the differences between the three groups for each task on RT showed that patients with persistent illness had significant RT deficits in the simple RT tasks compared to controls and to patients with fluctuating illness. Patients with fluctuating illness did not differ significantly than controls. These findings suggest that the

underlying neurobiological processes necessary for attention and initiation are impaired in patients with persistent illness, but remain intact in patients with fluctuating illness.

The forced choice RT task differed from the simple RT task in that, in addition to attending to a stimulus and initiating a response, the subjects were required to make a dichotomous decision (left or right) depending on the stimulus presented. With this additional level of processing, the patients with fluctuating illness were significantly slower than normal controls. In contrast, in the simple RT tasks, the performance was not significantly different between the two patient groups. This suggests that patients with fluctuating illness have impairments in the physiological processes associated with dichotomous decision making or information processing beyond those necessary for attention and initiation.

In accordance with prediction, negative symptoms were correlated with the simple RT tasks (initiation) in patients with persistent illness, but this correlation was weaker in patients with fluctuating illness. Disorganization was significantly correlated with performance on the forced choice RT (response selection) in both persistent and fluctuating illness groups. Patients with persistent illness, negative symptoms and impaired initiation reflect subtle but chronic malfunctions of the circuits responsible for initiation of activity (Ngan & Liddle, 2000).

The study of Vinogradov et al (1998) used a lexical decision choice reaction time (CRT) task, to explore the relation of mean CRT and its IIV (CRT-SD) to psychiatric symptoms and to performance on executive-motor tasks in 26 medication-free schizophrenic out-patients and 17 normal subjects. Schizophrenic subjects had both significantly slower and more variable CRTs which were unrelated to general intellectual abilities (IQ). Among schizophrenics, both CRT and CRT-SD were significantly related to severity of psychotic symptoms, failure to maintain cognitive set, and poorer motor coordination and global functioning. After controlling for mean CRT, CRT-SD showed unique covariation with clinical symptoms (positive, disorganized and tension/hostility). Mean CRT showed unique covariation with the failure to maintain a cognitive set and with stereotypic mannerisms, independent of CRT-SD. These results suggest that slower CRT and increased IIV in CRT reflect separate aspects of symptomatic and cognitive dysfunction in SZ (Vinogradov et al, 1998). The CRT values in Vinogradov et al (1998) study were obtained as part of a lexical decision semantic priming experiment. The subjects were asked to press a

button when the target letter string presented on a monitor was a real word only. Since this was a priming experiment, target words were always preceded either by a semantically related prime or an unrelated prime with a stimulus onset asynchrony (SOA) of either 260 msec or 1000 msec. Targets were preceded by a preparatory stimulus, and 18 RTs were obtained in each of 4 different conditions for each subject. In this experiment, non-significant priming effects occurred only for paranoid subtype subjects and only in the 260 msec condition. The RTs (mean and SD) for each condition are reported for the two subject groups in the table 4.6.

Table 4.6 Sample characteristics: demographic profile and mean reaction time measures

	Normal controls (*N*=17)			**Schizophrenics (*N*=26)**	
Variable	Mean	SD		Mean	SD
Age (years)	37.8	7.7		40.2	9.6
Education (years)	15.2	1.4	*	13.9	1.7
Mean parental education (years)	14.2	4		13.9	3
Global assessment of functioning				50.6	11.3
Choice reaction times: four conditions (ms)					
260 ms SOA RT (unrelated prime)	479	53		577	88
260 ms SOA RT (related prime)	456	44		555	105
1000 ms SOA RT (unrelated prime)	493	68	***	607	104
1000 ms SOA RT (unrelated prime)	448	51		567	106
CRT: mean choice reaction time (ms)	469	50.6	***	577	93.2
CRT-SD: mean intra-individual variability in CRT (ms)	80.3	25.4	***	132	45.2
	N	%		*N*	%
Male gender	7	41		14	54
Caucasian race	12	71		15	58

Significant group differences by *t*-test (df=41) one-tailed *p<0.05; ***p<0.001 (Vinogradov et al, 1998)

All subjects were administered the Brief Psychiatric Rating Scale (BPRS). Each symptom was rated on a scale of 1–7. The internal reliability for positive symptoms (hallucinations, unusual thought content) was 0.83, for negative symptoms (emotional withdrawal, psychomotor retardation, blunted affect) was 0.84, and for tension/hostility (tension, hostility, uncooperativeness) was 0.67. All subjects were also administered the Motor-Signs Inventory (MSI), the Wisconsin Card Sort Test (WCST) and Shipley Institute of Living Scale. The MSI consists of 8 tests from the Neurological Signs Inventory which have localizing value for frontal and prefrontal dysfunction (Vinogradov et al, 1998).

For this study, Vinogradov et al (1998) used two of the motor tests: Fine Motor Coordination (finger tapping, finger opposition, heel–toe alternation, reciprocal pronation), and Sequenced Hand Shapes (fist–slap–edge). The WCST, a measure of executive problem solving, requires formation, maintenance and shifting of conceptual set in response to limited feedback. It shows sensitivity but not specificity to prefrontal dysfunction. The WCST indices used were: Perseverative Errors (number of errors due a failure to relinquish an incorrect rule), and Set-loss Errors (number of errors due to a failure to maintain a correct set). Failure to establish a correct set was calculated as Total Errors minus Perseverative and Set-loss Errors. The Shipley Institute of Living Scale is a brief, self-administered measure of general intellectual ability. Total score on the Shipley was used to estimate WAIS-R IQ.

Table 4.7 presents the clinical and the neurocognitive findings of the Vinogradov et al (1998) study. An ANOVA was performed on the mean CRTs in each of the 4 experimental conditions. It showed significant IIV among the mean CRTs in each condition for each subject group. An ANOVA on the CRT-SD for each of the four conditions found no significant IIV for the CRT-SDs between each condition (Vinogradov et al, 1998).

Table 4.7 Sample characteristics: clinical and neurocognitive data

	Normal controls (*N*=17)			**Schizophrenics (*N*=26)**	
Variable	Mean	SD		Mean	SD
Brief Psychiatric Rating Scale					
Conceptual Disorganization				3.3	1.4
Mannerisms				2.2	1.0
Positive Symptoms (3 items)				8.8	3.6
Negative Symptoms (3 items)				6.9	2.7
Tension/Hostility Symptoms (4 items)				9.8	2.4
Shipley IQ	111	6.3	*	98.9	12.8
Wisconsin Card Sort Test					
Total Errors	22.9	5.2	**	35.3	20.5
Set Loss	0.5	0.9	*	0.9	1.0
Perseverative Errors	11.6	7.2	*	19.4	2.9
Motor Signs Inventory					
Fine Motor Coordination	1.0	1.9	**	2.9	2.5
Sequenced Hand Shapes	2.4	1.6	*	4.0	2.9

Significant group differences by *t*-test (df=41) one-tailed *p<0.05; **p<0.01. CRT and CRT-SD were significantly intercorrelated in the schizophrenic group (r=0.66,N=26, p<0.001) and in the normal comparison group (r=0.66, N=17, p<0.004) (Vinogradov et al, 1998)

Slower CRT was related to GAF, conceptual disorganization, mannerisms and positive symptoms. Increased CRT-SD was associated with GAF, conceptual disorganization and positive symptoms. Increased CRT-SD also showed a significant positive association with tension-hostility symptoms.

Neither CRT nor CRT-SD was associated with IQ in schizophrenics or in normal controls. In the schizophrenic group, CRT significantly related to WCST Set-loss Errors and to fine motor coordination, while increased CRT-SD was significantly associated only with WCST Set-loss Errors. In the control group, neither CRT nor CRT-SD was significantly correlated with any cognitive measure (table 4.7).

In conclusion, the authors tested whether CRT-SD accounted for significant variance in the criterion measures, beyond that accounted for by CRT alone. Results found that CRT-SD accounted for additional significant unique variance beyond CRT in conceptual disorganization, positive symptoms and tension/hostility symptoms only. Thus, compared to normals, schizophrenics showed slower CRT and higher IIV in CRT (CRT-SD) on a lexical decision task. In the schizophrenic group, slower CRT was related to lower GAF, greater conceptual disorganization, more stereotypic mannerisms, and higher positive symptoms. These results are consistent with other studies, which have suggested an association of slower RT with global functioning and psychotic symptoms. Increased CRT-SD was also related to lower GAF scores and higher conceptual disorganization, positive symptoms and tension/hostility.

To determine whether the manual RT time impairment could be eliminated by providing imperative stimuli to the finger (thus providing stimulus–response compatibility), Gale and Holzman (2000) tested 28 chronic schizophrenics on finger-lift RT to visual (VIS), tactile plus visual (TAC+VIS), and auditory plus tactile plus visual (AUD+TAC+VIS) stimuli. The patients (a) were significantly slower than controls (*n*=28) in all three tasks, (b) results showed bimodality, with 43% of patients having means and variances nearly identical to control values, and (c) patients had RTs significantly closer to control values in the TAC+VIS and AUD+TAC+VIS tasks than in the VIS task. The inability to normalize finger-lift RT in SZ represents a genuine slowing of this response system regardless of stimulus–response compatibility.

In summary, Gale & Holzman (2000) tested the effects of varying the sense modality of high-intensity stimulus presentations on SZ patients' finger-lift RTs to examine the relation between the sensory modality of stimulus presentation and the response.

Their results indicated that finger-lift RT in SZ was not completely normalized in a paradigm that allowed for high-stimulus-response compatibility (use of a tactile stimulus). For both SZ patients and normal control participants, the combination of an auditory, tactile, and visual stimulus did not produce a statistically significantly faster RT than a task using both tactile and visual stimuli. Also, the high intensity stimuli presented in all three modalities simultaneously (AUD+TAC+VIS task) did not normalize RT in the SZ patients, nor did it improve RT in SZ patients than controls when compared with RT in the task using tactile and visual stimuli (TAC+VIS task). Also, in both SZ and control subjects, when tactile or auditory-plus-tactile stimuli were added to the visual stimulus, RTs were considerably faster compared with RTs to the visual stimuli alone.

SZ patients, however, showed a greater absolute improvement in RT than controls when tactile or auditory-plus-tactile stimuli were used in conjunction with the visual stimulus (fig 4.9, Gale & Holzman (2000). In both schizophrenics and controls, higher visual RT was significantly correlated with a greater decrease in RT when auditory and tactile stimuli were added to the visual. Testing the difference between the slopes of SZ patients and controls showed no statistically significant difference. The relation between simple visual–manual RT and the RT reduction due to the addition of tactile and auditory stimuli was equivalent in both groups. The authors reported that the greater reduction in RT in SZ on the AUD+TAC+VIS task compared with the VIS task was a function of increased RT in general (Gale & Holzman (2000).

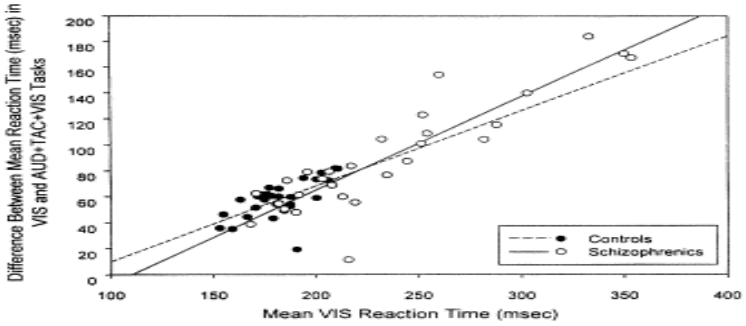


Fig.4.9 Scatter plot of mean RT in VIS task versus the difference in mean RT between the VIS task and the AUD+TAC+VIS task, for each subject (*N*=56). The solid and dashed lines are the least-squares line of fit for the schizophrenia patients (*n*=28, open circles) and the control subjects (*n*=28, filled circles), respectively (Gale & Holzman, 2000)

Gale & Holzman (2000) calculated the differences in RTs to different stimuli, based on peripheral sensory processes. They thought that there should be a maximum difference between visual and auditory (or tactile) RT of 30msec. Actual mean difference obtained was 57.7msec for the control subjects and 90.5msec for SZ patients. If differences between visual and auditory RT were based purely on differences in the sensory processes, a constant RT difference across the RT spectrum for all groups would be expected. Fig 4.10 presents a scatterplot of the relation between mean TAC+VIS RT versus mean AUD+TAC+VIS RT (*r*=0.88), and Fig 4.11 presents a scatterplot of the relation of mean VIS RT versus mean AUD+TAC+VIS RT (*r*=0.84).

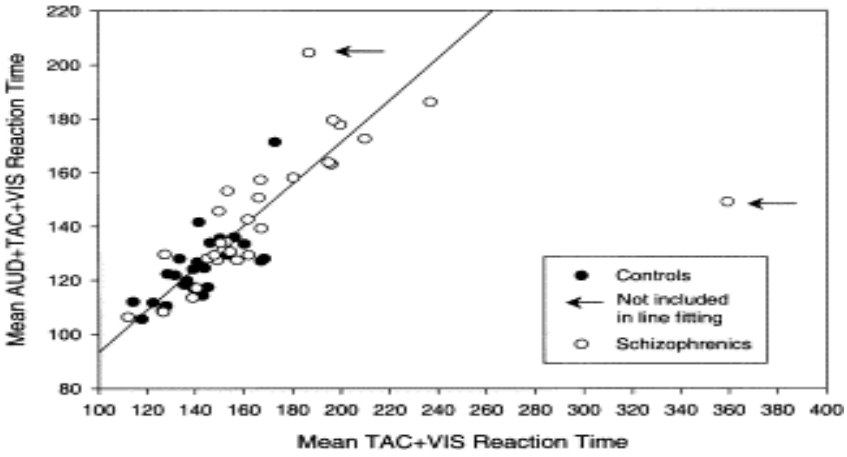


Fig. 4.10 Scatter plot of each subject's mean RT for the TAC+VIS task versus their mean RT for the AUD+TAC+VIS task. The line on the plot represents the least-squares line of fit, with one subject excluded (marked by arrow) because the data yielded a high residual and acted as a high-lever. *N*=55, *r*=0.88, slope=0.779, *y*-intercept=15.45 (Gale & Holzman, 2000).

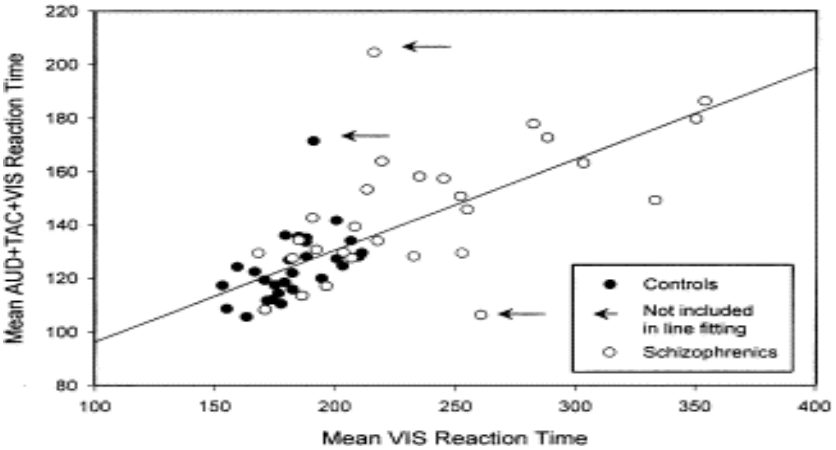


Fig. 4.11 Scatter plot of each subject's mean RT for the VIS task versus their mean RT for the AUD+TAC+VIS task. The line on the plot represents the least-squares line of fit, with three subjects excluded (marked by arrows) because their data yielded a high residual. *N*=53, *r*=0.84, slope=0.342, *y*-intercept=62.23 (Gale & Holzman, 2000)

Gale & Holzman (2000) divided the SZ group into two subgroups: (a) Sz-HI RT, SZ patients whose mean RT was higher than the highest mean control RT on at least one of the three tasks (a grouping of patients who were higher on two or more tasks proved nearly identical); and (b) Sz-NORMAL RT, patients whose RT was at or below the highest control RT on all three tasks. Table 4.8 compares these two SZ subgroups with the normal controls on the VIS RT task.

Table 4.8 RT and subject variance for SZ patients (divided into two groups) and for control subjects (Gale & Holzman, 2000)

Group	*N*	Mean VIS RT (S.D.)	Mean of individual subject variance for VIS RT
Controls	28	182.3 (15.84)	2441
Sz-NORMAL RT	12	192.0 (15.05)	2312
Sz-HI RT	16	268.0 (46.13)	13 092

Although the Sz-HI RT subgroup clearly exceeded the controls in mean VIS RT, and in their within- and between-subject variance, the Sz-NORMAL RT subgroup is essentially identical to the controls on all measures; the difference between controls and the Sz-NORMAL RT subgroup, for mean VIS RT, did not reach statistical significance [$t(38)=1.799$, $P<0.080$). Investigating eye tracking or RT, there were group differences *within* the SZ group, and there were instances when an individual's own typical or mean performance was interrupted or degraded temporarily, a phenomenon termed *dialipsis* (Gale and Holzman (2000). There were thus two mixtures in the SZ group, one referable to group membership and the other to the appearance of *dialipsis*. This model recognized that not all SZ patients showed degraded performance, and those who did, might not show that abnormal performance all of the time. Intermittent degradation in SZ patients' performance suggests that even in the 'good' SZ group there may be several with occasional dialipses. Gale & Holzman (2000) also found that just over half (57%) of the SZ patient group account for the slowed RT, with the remainder appearing normal in RT.

The study of Gale & Holzman (2000) was inspired by the facts that schizophrenics show slowed finger-lift RT but saccadic RT to visual stimuli appears to be normal. Both saccadic and manual RTs reflect the speed with which a voluntary motor response is made to the onset of a sensory signal. The researchers speculated that the explanation for their contrasting findings was the fact that saccadic responses to visual stimuli were highly compatible. The typical finger-lift RTs,

however, involve different modalities for stimulus and response. The study showed that manual RT in SZ is not reduced to normal levels by the use of what appears to be a highly compatible stimulus-response paradigm. Therefore, the saccadic response to a visual stimulus seems to be unique (Gale & Holzman, 2000).

Neural mechanisms of IIV

Theories present that the increased IIV in SZ could be due to a deficient neural timing mechanism.

Kaiser et al (2008) compared IIV measures obtained in a Go/Nogo task from patients with SZ, major depression and borderline personality disorder. As expected, IIV was increased for patients with SZ. Depressive and borderline patients also showed increased IIV. All groups showed a strong association between IIV and accuracy of task performance. This suggested that increased IIV might be a sensitive marker for the efficiency of top–down attentional control in all diagnostic groups. Apart from the similarities in IIV results, mean RT and accuracy showed differential patterns for patients with SZ compared to those with borderline personality disorder or depression (Kaiser et al, 2008).

Kaiser's et al (2008) study was the first study to compare RT IIV between three psychiatric patient groups and healthy controls. Increase in IIV was specific to patients with SZ and differentiated them from patients with depressive or borderline personality disorder. This is in line with the rest of the literature, where an increase in IIV has been repeatedly reported mostly for schizophrenic patients (Vinogradov et al, 1998, see above). Schizophrenics also showed slower RTs than the other groups and there was a correlation between mean RT and individual SD. In Kaiser's et al (2008) opinion, when both a correlation between individual SD of RT and mean RT as well as group differences in mean RT are observed, it is necessary to report the coefficient variation (CV) along with the individual SD as measures of IIV.

Functional imaging studies have reported positive correlation between IIV and activation of prefrontal areas related to attentional control (Kaiser et al (2008). This was interpreted as increased requirement for executive control in subjects with higher CV. A popular neurocognitive theory of SZ also postulates a deficient neural timing mechanism due to disruption of cortical-thalamic-cerebellar-cortical circuits (Andreasen et al, 1998).

Kaiser's et al (2008) data are consistent with the cognitive dysmetria model suggesting disruption of the cortico-thalamic-cerebellar-circuits. These circuits which serve attentional control are thus critically affected. Impairment of catecholaminergic neurotransmission is also considered as a cause of increased IIV.

A dysregulation of catecholaminergic modulation of the frontal lobe has also been put forward to explain increased IIV in patients with ADHD (see also above). Besides, there is a strong association between IIV and task performance. This suggests that IIV indexes efficiency of top-down attentional control (Kaiser et al, 2008).

As many studies showed so far, sustained attention is definitely affected by SZ. The CPT-X is a purer test of vigilance than other more demanding variants but is also thought too insensitive to detect abnormalities in those with genetic predisposition to SZ.

Birkett et al (2007) used a 7-minute CPT-X to compare 61 patients diagnosed with SZ, 45 of their never-psychotic relatives, and 47 control subjects. The authors found a significant impairment in stimulus discrimination in both patients ($p = 0.001$) and their relatives ($p = 0.006$). Relatives of patients with unimpaired stimulus discrimination were still inferior to controls ($p = 0.02$). RTs slowed in all groups equally as the test progressed. Patients showed increased mean RT ($p < 0.0001$) and interquartile range ($p = 0.003$). Relatives showed slower RTs ($p = 0.01$) but normal interquartile range (fig 4.12, 4.13, table 4.9). The groups did not differ in respect of individuals' fastest RTs. Birkett et al (2007) concluded that genetic predisposition to SZ reduces performance even during a task placing minimal cognitive load on WM and perceptual processing, suggesting impaired vigilance. Increased RT in the disease is due to changes in response distribution rather than to a limitation of maximum speed (Birkett et al, 2007).

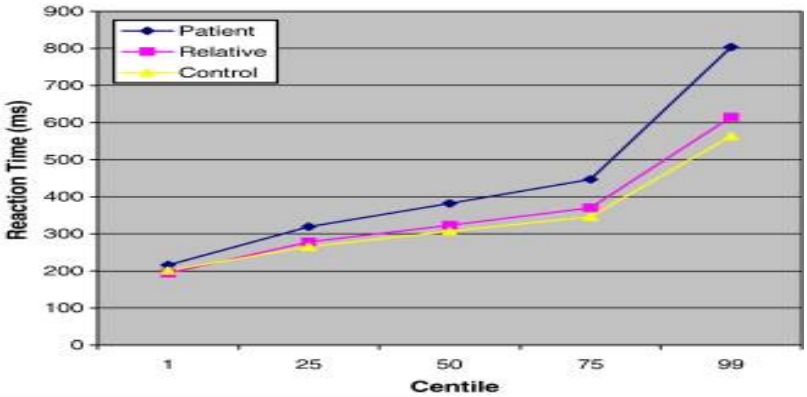


Fig 4.12 Cumulative reaction time distribution (Birkett et al, 2007)

Table 4.9 Reaction time distribution (ms)

Centile	1	25	50	75	99
Patients	216	319[a]	382[a]	447[a]	804[a]
Relatives	194	278	323[b]	370[b]	615
Controls	201	265	307	346	564

Significance values are for comparisons with controls. a $p \leq 0.0001$., b $p \leq 0.05$ (Birkett et al, 2007)

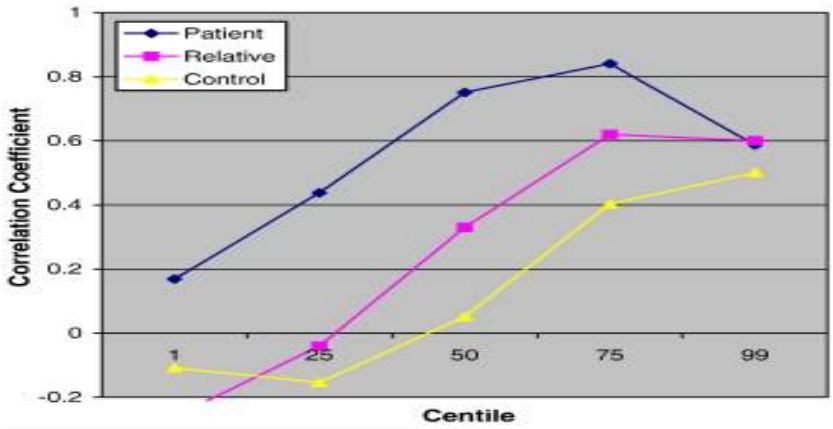


Fig.4.13 Correlation with interquartile range (Birkett et al, 2007)

The authors have shown that the CPT-X can detect vigilance abnormalities in those at increased genetic risk of SZ. WM and perceptual processing should be tested separately as they have a different cognitive basis and possibly also a different genetic basis (Birkett et al, 2007).

Vinogradov et al (1998) (see above) found IIV in a group of schizophrenics, associated with psychotic symptoms, disorganization and tension/hostility, while mean RT was associated with stereotypy and failure to maintain set. As already mentioned, increased IIV has been shown in ADHD patients and in patients with traumatic brain injury as well. Birkett et al (2007) showed greater IIV in performance in subjects with lower intelligence. Beyond doubt, IIV is not specific for SZ.

The authors have also shown that SZ has little effect on patients' fastest RTs but progressively more effect on slower RTs. This might be a “ceiling effect”. This is an artefact caused by a physiological lower limit on subjects' RTs, but there is considerable variation within groups. There is little correlation with the fastest RTs, but progressively higher correlations with slower RTs. Similar patterns have been seen in ADHD. Thus, the “ceiling effect” is not specific to SZ either.

CHAPTER FIVE – Saccades in SZ

The oculomotor system

The oculomotor system is responsible for three types of movements: saccadic movements, smooth tracking movements (smooth pursuit movements) and convergent-divergent movements (vergence movements).

Saccadic movements (saccades)

They are voluntary eye movements (more than 100,000 daily) with which we "scan" an image. They are the most rapid movements of the human body (~ 700th/sec) and very short (~ 50 msec). The amplitude and the direction are voluntary. Their speed is involuntary, determined by the eccentricity of the object (Vrettos, 2006).

Smooth tracking movements (smooth pursuit movements)

These are movements with which we can follow a moving object in our visual field. Their top speed is ~ 100 °/sec (lower than that of the saccades). They are controlled by the speed of the moving object (Vrettos, 2006).

Convergent-divergent movements (vergence movements)

They are "uncoupled" eye movements where the eyes converge (convergence), during the adjustment, or diverge (divergence) from each other. They take place when an object approaches or turns away, respectively. They are guided by the degree of dissimilarity of the retinal image (the object image is displayed on different areas in each eye (retinal disparity).

The stabilizing system

The stabilizing system is determined by the eye movements that take place during fixation to a stable point. It is responsible for three types of movements. These are the shaking movements (tremors), the sliding movements (drifts) and microsaccadic movements (microsaccades).

Shaking movements (tremors)

These movements are often called physiological nystagmus. They are involuntary oscillatory movements of one or both eyes capable to maintain neurons in continuous operation. They are essentially aperiodic conjugated eye movements with a frequency of ~ 90 Hz. They are the smallest eye movements with a width approximately the same as the diameter of a cone in the fovea region (~ 0.5arcmin). It is quite difficult to record them accurately as their widths and

their frequencies are usually in the noise range of the recording system. Their contribution to the support of vision is still unclear. They are independent of both eyes and may limit the ability of the visual system to combine information from the two retinas (Vrettos, 2006).

Sliding movements (drifts)

They are slow curved movements which take place simultaneously with the tremor movements in the period between microsaccadic movements. During the sliding movements (drifts), the target image "slips" through 5-15 photoreceptors. They are recorded as conjugated and as non-conjugated. They are thought to be due to the instability of the oculomotor muscles and the displacement of the image from the fovea due microsaccadic movements (Vrettos, 2006).

Microsaccadic movements (microsaccades)

The microsaccades are small, abrupt, involuntary movements that occur during fixation. They virtually carry the retinal image through a few tens of photoreceptors. The amplitude of motion is between 5-120 arcmin. Their frequency is 0, 1-5 Hz. They last approximately 25ms. Their role is to correct eye movements which are produced by the drifts.

The saccadic movements are controlled by two areas of the brain stem, the control region of the horizontal movement located in the pontine reticular formation (PRF), near the core of the duct and the control region of the vertical movement (IMLF) which is within the mesencephalic reticular formation near the nucleus of the oculomotor nerve (Vrettos, 2006). There is cooperation of these areas with the nuclei of the anterior colliculus, with the frontal BA 8 and with the third and sixth cranial nerve. PPRF consists of inhibitory neurons (pausers), pontine nuclei raphe excitatory neurons (reticular burst neurons) and tonic pontine neurons.

Eye movement dysfunctions in psychiatric patients

Eye tracking pattern is under genetic control and impairments reflect a predisposition to functional psychosis. The smooth pursuit eye movement impairment has been attributed to a CNS dysfunction, a disorder of non-voluntary attention (Lipton et al, 1983).

Smooth pursuit dysfunction and psychiatric diagnosis

It was reported that impaired pursuit was characteristic of SZ. Tracking dysfunction though was not limited to schizophrenics. Eye tracking impairments with qualitative similarity to those observed in SZ also occur in diseases of the CNS, as well as in certain drug-induced states.

A stronger association between SZ and disrupted pursuit was found when patients were diagnosed on the basis of the presence of thought disorder inferred from psychological test protocols than when symptoms were assessed according to DSM (1978) criteria (Lipton et al, 1983).

Prevalence of pursuit disruption

Holzman et al (1974) utilized diagnoses based on DSM-II (1978) criteria. The results suggested that the pursuit disruption was more strongly associated with a diagnosis of SZ (52-86%) than with either psychotic non-schizophrenic (22%) or non-psychotic syndromes (21%). In a later study designed to minimize clinical heterogeneity they reported on a sample of 32 patients who met the Washington University criteria for SZ or manic depressive illness. Half the patients with functional psychoses had smooth pursuit dysfunction, regardless of specific diagnosis. Thus, smooth pursuit impairment is not specific for SZ (Lipton et al, 1983).

Family studies

Holzman et al (1974) reported that schizophrenics and their first-degree biological relatives accounted for over 80 % of the abnormal pursuit in a sample of over 200 subjects. Depending upon whether SZ was diagnosed by DSM-II or by psychological test criteria, 44 to 55%, respectively, of the family members of schizophrenics demonstrated qualitative disruptions of pursuit. Moreover, the quantity of thought disorder was significantly associated with eye tracking disruptions, both in patients and in relatives, suggesting a relationship between pursuit disruption and subclinical psychotic symptomatology. In addition, a high degree of intra-familial concordance for impaired pursuit occurred among schizophrenics and their relatives.

Twin studies

The prevalence of impaired pursuit in relatives of schizophrenics, and the association between subclinical manifestations of SZ and impaired pursuit, suggested a link between this oculomotor disturbance and inherited vulnerability to SZ. The prevalence of pursuit disruption was compared in a sample of monozygotic (MZ) and dizygotic (DZ) twins who were discordant for SZ (Lipton et al, 1983). Concordance for SZ was 18-36% among 11 MZ twin pairs and 0-13% among 15 DZ twin pairs, depending upon the narrowness of the diagnostic criteria (Lipton et al, 1983).

The prevalence rates of disrupted pursuit among 26 probands with diagnoses of SZ (69%) and among their 24 discordant co-twins (54%) were comparable to earlier results obtained in non-twin schizophrenics and their relatives. Pairwise concordance rates for qualitative measures of tracking were 71% and 54% among MZ and DZ twins, respectively. Among MZ twin pairs, but not among DZ sets, there was a significant tendency for quality of tracking to be alike (normal or abnormal) within a pair (Holzman et al, 1980).

There are currently four hypotheses about the eye movement dysfunctions. They may reflect: (1) artifacts of drug treatment and effects of age; (2) inattentiveness, heightened distractability, or lack of motivation; (3) CNS impairment; or (4) specific or general oculomotor dysfunction.

Saccadic RTs in acute and remitted schizophrenics

In the study of Mackert & Flechtner (1989), the saccadic RTs of 47 schizophrenic inpatients were investigated upon admission and later in the remitted state. 28 age- and sex-matched controls were tested. The Brief Psychiatric Rating Scale and the Prognostic Scale were used. Light stimuli were presented at random direction, location (ranging from 0° to 20°) and duration (800, 1000, and 1200ms). The eye movements were recorded by electrooculogram (EOG). Compared with the control group, schizophrenics revealed prolonged saccadic RTs, which correlated with negative symptoms and an unfavorable course of the illness. The saccadic RTs remained prolonged in schizophrenic patients. These findings suggest attentional deficits in schizophrenics (Mackert & Flechtner, 1989).

In agreement with many studies, schizophrenics had significantly prolonged saccadic RTs. There was no evidence of lateralization. The RTs were equally prolonged for saccadic eye movements to the left and right. Patients with negative symptoms were particularly characterized by prolonged RTs. There was evidence of a correlation between the extent of an unfavorable prognosis and RTs of saccadic movements.

Manual RTs have been investigated systematically in schizophrenics and have consistently been reported as prolonged (Nuechterlein & Dawson 1984, previous chapter). In contrast, there have been relatively few studies on ocular RTs, and some results have shown normal values. In these studies, testing saccadic RTs in schizophrenics, visual stimuli were changed slowly and were predictable either in time or location. Nuechterlein & Dawson (1984) emphasized that only

tasks with a high processing load would disclose deficits in schizophrenics. Since saccadic RT consists of sensory, motor and central processing components, it is considered to be a sensitive indicator of attentional impairment in central disorders.

Mackert & Flechtner (1989) also observed prolonged RTs mainly in patients with negative symptoms and poor prognosis.

Functional hemispheric imbalances in schizophrenics are well known. Testing of RTs to stimuli presented separately to the right and left visual field in schizophrenics, in comparison with the control group, disclosed prolonged RTs for both directions. The left hemisphere is assumed to be responsible for functions related to language and speech, whereas the right hemisphere governs visuospatial processes. Since the right hemisphere most likely contains the neural apparatus for attending to both the right and left spatial fields, delayed RTs in schizophrenics to stimuli presented to both right and left visual fields suggest that the source of the deficit might lie in the right hemisphere.

In the Mackert & Flechtner (1989) study, schizophrenics with delusions and hallucinations predominated. It might be expected that the acoustic hallucinations could cause a delay in the saccadic RTs because of easy distractability. However, schizophrenics characterized by hallucinations did not show disproportionally prolonged saccadic RTs. A relationship between poor outcome and prolonged RTs, particularly in patients with a long course of illness was found. Since patients with long and unfavorable courses of illness have often been receiving neuroleptics for many years, the effects due to their chronic state upon saccadic RTs cannot be separated completely from long-term neuroleptic medication. The delayed ocular RTs in schizophrenics were not related to age (Mackert & Flechtner, 1989).

Motion processing

Motion processing represents a perceptual domain in which dynamic visual information is encoded to support the perception of movement. Research over the last decade has found a variety of abnormalities in the processing of motion information in SZ. The abnormalities span from discrimination of basic motion features (such as speed) to integration of spatially distributed motion signals (such as coherent motion). Motion processing involves visual signals across space and time and thus helps to examine how spatial and temporal information is

integrated in the visual system. Chen (2011) reviewed the behavioral and neuroimaging studies that probe into the spatial integration of motion information in SZ. An imbalanced regulation of spatial interaction processes in SZ is suggested as a potential mechanism mediating different levels of abnormal motion processing. These studies suggest that investigation of the neural basis and functional consequences of abnormal motion processing may discover a basic biomarker for the schizophrenic cognitive dysfunction (Chen, 2011).

Speed is a salient visual feature that is uniquely encoded in the motion processing system. One empirical paradigm for studying the visual processing of speed signals is speed discrimination, in which perceptual judgments about two moving targets are rendered based upon respective speeds of the targets.

Deficient speed discrimination has been found in SZ. The perceptual problem is not related to the spatial contents (or forms) of the visual targets involved. The deficit is present not only in patients but also in their biological relatives, suggesting that the perceptual problem is not directly associated with clinical manifestations in patients. Also, the deficit is mostly prominent in intermediate speeds (10 degrees/s). Unlike slow speeds with which position cues are dominant or fast speeds with which temporal frequency cues are dominant, intermediate speeds are the conditions where speed cues dominate perceptual judgments of movements. Thus, the selective deficit in intermediate speeds indicates a perceptual problem specific to the motion processing (Chen, 2011).

Neural substrates for saccades

Neuroimaging has been applied to explore the neural substrates of motion processing in SZ. In an fMRI study, SZ patients showed decreased activation in medio-temporal (MT) and increased activation in the inferior prefrontal cortex during detection of coherent motion and speed discrimination, but not during contrast discrimination (Chen, 2011).

One limitation of the fMRIs is the relatively low resolution in the measurement of temporal dynamics, which is an evidently important aspect of motion processing. Studies showed MT activity during eye tracking of a moving target to be reduced in SZ patients and increased in posterior hippocampi and the right fusiform gyrus, or in the medial occipitotemporal cortex during patients' performance of an eye-tracking task (Chen, 2011).

RTs and saccades

In the past, Gale & Holzman (2000) reviewed all studies of visually guided saccades in SZ and concluded that the majority of these studies report that the mean RT in patients does not differ from that of controls.

But Smyrnis et al (2003) compared the RTs of visually triggered saccadic eye movements in a sample of 1089 young army conscripts to those of a sample of 53 patients with DSM-IV SZ. The authors used a simple method for deriving average RT distributions for the two groups and compared these RT average distributions. They also modeled the saccade RT distribution using the LATER model (Linear Approach to Threshold with Ergodic Rate) (Carpenter & Williams, 1995). The LATER model is shown in the fig. 5.1. The basic idea of the model is that the RT for making a saccade towards a visual target reflects a decision process in which a signal (decision signal) rises to reach a threshold. This signal reflects the accumulation of information for deciding whether the target is indeed present in order for the saccade to be made. When this accumulation of information reaches a criterion point S_T, the saccade initiates. This criterion point is reached at the level of certainty needed to confirm the hypothesis that the target is present at the particular location in space. The accumulation of information starts from a preset level of prior information S_0 that reflects prior knowledge about the presence of the target at a particular location in space (Carpenter & Williams, 1995). The accumulation of information *r* is considered to be linear with rate *r*, which varies from trial to trial. This variation of rate has a normal distribution across different trials with mean μ and variance σ (fig.5.1). The basic prediction of this model then is that the distribution of the reciprocal of RT, which is equal to *r* (fig. 5.1), is normal with mean μ and variance σ.

Carpenter showed that although the distribution of saccadic RTs is skewed, the distribution of the reciprocal of RT is normal. The model also makes explicit predictions on how the RT distribution will be affected by specific manipulations such as, for example, a change in prior probability for target location S_0 or the change in the criterion S_T needed for a response or the mean rate of accumulation of information μ. All these manipulations have been tested and the predictions of the model were verified experimentally (Smyrnis et al, 2009).

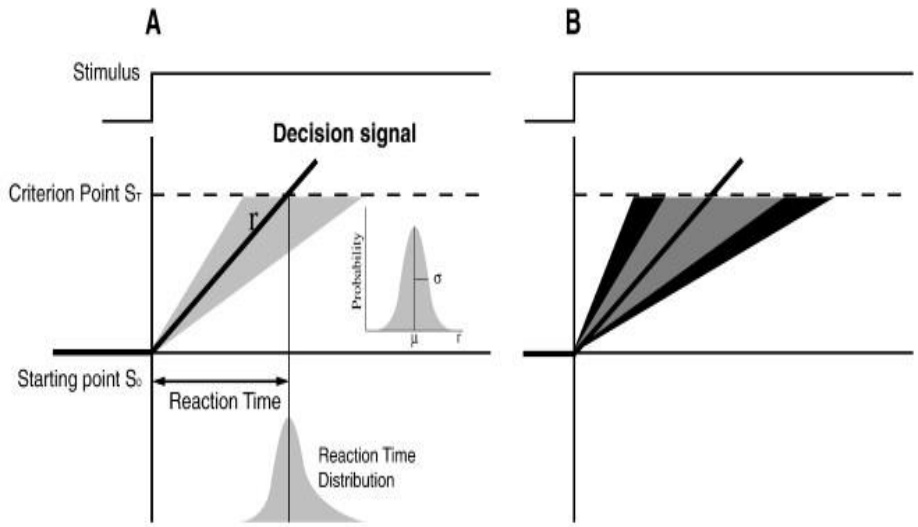


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Fig. 5.1. A: A decision signal, depicted by the heavy black line in the figure, evolves linearly from a starting point (S_0) when the visual stimulus is where a criterion point (S_T) were a decision is made to saccade to the stimulus. The rate of this linearly increasing decision process *r* is thought to vary from trial to trial and this variation is modeled as a normal distribution with a mean μ and variance σ (shaded area around μ). The RT for a particular trial is equal to (S_T–S_0) / *r*. This decision process can explain the shape of the RT distribution that is skewed to the right.
B: The model prediction is that the decision signal in the patient group will be more variable from trial to trial (larger σ) than the decision signal in the control group (gray area represents the σ for controls and the underlying black area represents the σ for patients (Smyrnis et al, 2009)

The model predicts that neuronal activity in areas of the brain that contribute to the generation of visually guided saccades might follow the same pattern as the decision signal.
Previously, rhesus monkeys performed saccades to visual targets while the activity of single neurons in the frontal eye field was recorded. A neuron's firing rate increased linearly during the RT to reach a maximum firing rate after which the saccade was initiated. The maximum frequency did not change from trial to trial and thus could not predict differences in RT from trial to trial. In contrast the rate of the increase in the firing frequency changed from trial to trial as predicted by the model (fig 5.1). This variation in firing frequency predicted very well the variation in RT from trial to trial. This study showed that indeed the decision signal *r* of the model could be related to the firing rate of single neurons in the frontal eye field.
In a recent study, fMRI was used in humans. The study correlated the hemodynamic response during an anticipation period before the execution of a visually guided saccade to the RT for that saccade on a trial by trial basis. The investigators observed that the higher this preparatory activity in the contralateral frontal eye field, the shorter the RT of the subsequent saccade. This

relation was significant only for the contralateral frontal eye field. Thus, both in animals and in humans, the rate of the rise of neuronal activity before the execution of a visually guided saccade predicts the RT of that saccade. The authors used the LATER model (fig.5.1) in the analysis of the RT distributions of patients with SZ and controls. The application of the model helped the explanation of the information-processing difference between patients and controls which underlies the variations in the RT distributions. It pointed to a neuronal substrate for this information-processing difference (Connolly et al, 2005).

The results of the Smyrnis et al (2009) study provided evidence in favor of the hypothesis that there is indeed a specific difference between patients with SZ and controls in the RT distribution, and this difference is present in a simple task in which there is no large psychomotor slowing. The increase in the mean saccadic RT for patients with SZ was significant after controlling for age differences between controls and patients. In contrast to the small increase in mean RT, there was a highly significant increase in the variability of RT in the patient group that was confirmed in the significantly larger CV for this group (an increase of 35% compared with the CV for controls). This difference between patients and controls was confirmed by the LATER model for RT distribution. The model parameters were significantly different for patients than for controls. Thus, the difference in the shape of the RT distribution in SZ might be a core difference linked to performance deficits in these patients. The application of the LATER model (Carpenter and Williams, 1995) to the authors' data showed that patients with SZ have larger variability in the rate of rise of the decision signal from trial to trial, while the threshold and the mean of that signal do not differ from those of controls.

Many models of RT distributions have been employed in the literature. The best known alternative model to the LATER model for simple RT tasks is the diffusion model (Diederich & Busemeyer, 2003). This model can be applied to simple RT tasks. A decision signal rises to a threshold and this reflects the time of the RT in the same fashion as in the LATER model. The major difference between the two models is that the rise of the decision signal in the diffusion model obeys a stochastic process that represents the accumulation of information available to the decision mechanism at any given time while the process in the LATER model is a deterministic one and obeys a simple linear process with a mean rater.

The authors [Smyrnis et al (2009)], for this study, chose to model their data using the LATER model. The first reason for this choice is the simplicity of the LATER model compared with the more complicated diffusion model. Another reason is the fact that the LATER model was proved to be superior to the diffusion model when simulating the decision process for generating a saccade to a supra-threshold stimulus that is very easily detected (Carpenter, 2005). Also, the LATER model has already been tested neurophysiologically in a simple saccade RT task. It was found that the activity of the frontal eye field neurons of the monkey followed the predictions for the decision signal of the model (Hanes & Schall, 1996).

Theleritis et al (2014) studied RTs of visually guided saccades in young healthy men, healthy children, older adults, patients with SZ, and patients with OCD in order to investigate the specificity of decision process deviance for SZ. The mean decision rate to saccade decreased with age in children and increased in older adults while the decision rate IIV was not modulated by age. A significant increase in IIV of the decision rate was confirmed for patients with SZ but not OCD compared to healthy controls. The results from the Theleritis et al (2014) study confirm the specificity of the deviance in a simple oculomotor decision process in SZ. In the study of Theleritis et al (2014), although mean RT for visually guided saccades was not larger for patients with SZ, when the IIV of the RT distribution was measured, a different picture emerged, i.e. an increase of IIV of RT for saccades for patients compared to controls (Smyrnis et al, 2009). In order to provide a quantitative description of the characteristics of the RT distribution in the Theleritis et al (2004) study, the LATER model was also applied. The LATER model operates as described above. In a previous study (Smyrnis et al, 2009, see above), the application of the LATER model to the averaged RT distributions of patients with SZ and controls showed that the mean rate of rise of the decision signal mu was not different, suggesting that the same threshold for decision was present for both groups. In contrast, patients with SZ had a significantly larger sigma, suggesting that the rate of rise r of the decision signal was more variable for these patients. In a recent study, Smyrnis et al (2012) also showed that, in a visuomotor RT task in healthy volunteers, the rate of rise of the MEG activity in the motor area before movement onset was highly correlated with sigma. Sigma seemed to be directly related to the variation of the activation rate of the motor areas of the brain.

The first aim of the study of Theleritis et al (2014) was to explore the specificity of the deviance in information processing for schizophrenics evidenced in the larger sigma of the saccadic RT distribution. The saccadic RT distributions of patients with SZ, patients with OCD, and healthy controls were analyzed using the LATER model to estimate mu and sigma for the RT distribution of each participant (Theleritis et al, 2014). The second aim of this study was to explore whether the increase in the variation sigma of the saccadic RT distribution observed in SZ could be linked to the developmental changes of the saccadic system from childhood to adulthood or to the changes in the function of this system from adulthood to old age. In order to analyze the RT distribution for each subject, they used the SPIC (saccadic program and instrumentation computer) which runs saccadic latency experiments, presents stimuli, records eye movements, detects saccades in real time and analyses saccadic latency data (Theleritis et al, 2014).
The series of RTs for each subject were entered in the SPIC analysis software, and then the LATER model was fit to the RT data. The LATER model predicts that if the cumulative saccadic RT distribution is plotted using 1/RT instead of RT in a probit scale (a "reciprobit" plot), the RTs will fall on a straight line. The SPICS program computes the best-fitting regression line in the cumulative distribution data of RT in a reciprobit plot. It also has the option of computing a separate line for the very early RTs of each subject that are modeled to bypass the decision process. These RTs then have a slope with a mean mu of zero (no decision process) and a variance sigma-early. The authors retained this second early RT fitting slope only if the resulting model had a better fit than the original model.

LATER model parameters and descriptive RT distribution measures (table 5.1)

The table 5.1 presents the correlations of the mu, sigma, and sigma-early (only for cases where an early component was observed) LATER model parameters and the descriptive statistics of the RT distribution for each individual of the young control group (median, interquartile difference, CV). The mean slope of the decision signal modeled by mu was highly negatively correlated with the median RT as expected by its definition. The trial-by-trial variation of the decision signal slope modeled by sigma was highly positively correlated with the CV of the median RT that reflects the trial-by-trial variation of RT normalized to the median RT. The presence of an early RT slope was significantly correlated only with the percentage of express

saccades, and the highest correlation of express saccade proportion was with the dispersion sigma of this early slope.

	Median RT	Interquartile RT difference	RT coefficient of variation	Percent of express
Note. Pearson correlation coefficients are presented. In the cases of the correlations with the sigma-early parameters, only the subgroup of 29 subjects with an early LATER component was used. Significant correlation coefficients at $p < .05$ are marked in bold.				
Mu	**−.97**	**−.65**	**−.38**	.22
Sigma	**−.29**	**.40**	**.61**	.24
Early	−.13	.12	.08	**.43**
Sigma-early	−.18	**.41**	**.51**	**.76**

Table 5.1 Correlations of LATER model parameters and descriptive RT distribution measures in the young control group (Theleritis et al, 2014)

Gender effects on LATER model parameters (table 5.2)

The children and older groups had gender variation while all other groups included only male subjects. Thus, before the analysis of group differences, the authors tested for gender differences of all variables of interest within each of these groups, and the results are presented in table 5.2. As it can be seen, there were no significant gender differences for all variables measured, so Theleritis et al (2014) pooled data for male and female subjects within each group for all subsequent analyses.

Subjects	Male mean (SD)	Female mean (*SD*)	*t* value (*df*)	*p*
Note. Gender differences were tested with a *t* test except for the percentage of subjects with an early RT slope where a test for percentage differences was used. Median RT = mean of the median RT values (measured in ms) for all subjects in each group. Model mu = mean rate of the LATI model decision process mu. Model sigma = variance of the rate of the decision process. Early = percentage of subjects for which the LATER model included an early RT slope (where RT bypassed the decision process). Sigma-early = variability of the early slope only for subjects for which such a slope was present.				
Children				
Model mu	5.5 (1)	5.4 (0.9)	0.47 (35)	.64
Model sigma	0.99 (0.16)	0.93 (0.19)	0.94 (35)	.35
Early (%)	52.6	45.5	–	.63
Sigma-early	5.1 (1.1)	4.1 (1.5)	1.59 (17)	.13
Older				
Model mu	5.9 (1)	5.6 (0.93)	0.2 (65)	.84
Model sigma	1.09 (0.32)	1.01 (0.3)	1.7 (65)	.1
Early (%)	51.4	37.5	–	.26
Sigma-early	5.9 (1.6)	5.5 (2.4)	0.55 (28)	.58

Table 5.2 Gender differences in LATER model parameters (Theleritis et al, 2014)

Effects of psychopathology

The analysis of variance in Theleritis et al (2014) study showed that the mean rate of the increase of the decision process mu of the LATER model did not differ among the young, SZ, and OCD groups. The trial-by-trial variability in the increase of the decision process reflected in sigma differed significantly among groups. Patients with SZ had higher sigma values compared to young control adults and OCD patients. Comparisons showed that the significant difference was between the young adult control group and the SZ patient group. The percentage of subjects with an early RT sub-process component in the LATER model was 58% in the young control group, 51% in the SZ group, and 47% in the OCD group. These percentages did not differ among groups. The variability of the early slope, sigma-early also did not differ among groups. There was no effect of medication on mu or sigma.

Effects of psychopathology and medication

The study of Theleritis et al (2014) also showed that the increase in the variability of the decision signal leading to a saccade was specific for patients with SZ and did not dissociate patients with OCD from controls. The specificity of a measure of IIV RT variability to dissociate patients with SZ from patients with other psychiatric syndromes was also observed in previous studies. A specific increase in RT IIV in manual RT tasks was also found in patients with SZ (Vinogradov et al, 1998). It has also been suggested that the increase in RT IIV in SZ might also be hereditary.

In contrast to SZ, where RT distribution has not received attention in the past, it has been of major interest in the research of ADHD. The IIV in RT reliably dissociated individuals with ADHD from controls independently of the cognitive task where RT was measured.

The study of Theleritis et al (2014) suggests that the increase in the RT IIV in SZ is also evident in the saccadic system. Also, the patients with SZ differ from healthy controls in the most simple decision process, i.e. the decision when to begin a saccadic eye movement to a visual stimulus. The decision-making behavior in SZ appears to be deregulated, and characterized by intermittent switching between highly predictable and highly unpredictable actions (Paulus & Braff, 2003). This intermittent behavior is observed even at the most basic level of decision

processing. It offers a model for studying the neurophysiological basis of the deviance in decision processing.

In the study of Theleritis et al (2014), the early component of the RT distribution did not dissociate patients with SZ from controls. Since previous studies showed that patients with SZ make more express saccades than normal controls, one would predict that the presence of an early LATER component would be more prominent in these patients indicating a deficiency at the cortical control of saccades. This was not verified by the authors' results. One potential explanation for these discrepant results could be that the increase in the variability of the decision process in schizophenics could result in an increase in the number of saccades with fast RT within the predefined range of 80–120ms (express saccades) as well as an increase in the number of slow saccades. One factor for the difference in sigma between patients with SZ and controls could have been the medication status. But in the study, all the patients with SZ were medicated with antipsychotics. Thus, it could not be tested whether differences in sigma for these patients were or not related to the effects of medications.

Effects of maturation

The second objective of the study of Theleritis et al (2014) was to compare the differences in the saccadic performance of SZ patients and controls as assessed by the LATER model to the differences observed in the maturation of the saccadic system from childhood to adulthood and the differences observed in the saccadic system with aging. As already mentioned, older adults had a higher mean sigma compared to young adults and children, but none of these differences reached significance. A more sensitive analysis of age effects within each group revealed significant effects of age in the children and older adult groups but not the young adult group where age effects were absent.

Since the pattern of changes observed differed in the children and older adult groups, the dissociation of the effect of maturation from the effect of aging on saccadic RT distribution was allowed. The only LATER parameter that varied with age in the children group was the mean rate of the decision process mu. Decision rate increased with age, reflecting a decrease of median saccadic RT. No other RT distribution parameter varied significantly with age.

CHAPTER SIX DISCUSSION

SZ affects millions of people worldwide and occupies most of the hospital beds. The symptoms of the disease are many, variable and exhausting, leading to personal disorganization, work deterioration and social drifting. The fact that SZ presents with such a variety of symptoms led to the hypothesis that it may not be a single disease but a group of disorders. Many efforts have been made to find a reliable diagnostic and/or prognostic test. There is definitely need for a test that would diagnose SZ reliably and would predict the disease long before its appearance. If such a test could also identify all the family members at risk, it would have also been most welcome.

Genetic studies are taking place and so far many candidate genes have been evaluated but none so far can be acclaimed as the exact cause of the disease. Apart from the direct DNA studies, knockout animals are being extensively used as possible experimental models for SZ. Despite all the scientific efforts, the disease so far holds its secrets well hidden. Thus, neither prevention nor treatment is etiologically driven and basically the disease is considered incurable, only alleviated by the continuous use of antipsychotic medication. Due to the patient's lack of insight, treatment is discontinued very easily with major relapses of the disease's symptoms and frequent hospitalizations.

A variety of neuropsychiatric disorders have associations with frontal-subcortical circuit dysfunction, especially SZ. SZ has been associated with frontal lobe dysfunction as well as abnormal regulation of subcortical DA systems (Goldman-Rakic & Seleman, 1997). Functional imaging studies in patients with SZ, show decreased cerebral blood flow in the dorsolateral prefrontal cortex during a variety of cognitive tasks (Andreasen et al, 1994). Frontal lobe glucose utilization is also decreased in SZ patients with prominent negative symptoms (Tamminga et al, 1992). Neuroanatomical postmortem findings and structural imaging studies reveal a reduction in the cortical volume in patients with SZ (Breier et al, 1992).

Neurochemical markers in the dorsolateral prefrontal cortex and hippocampal region are decreased in SZ patients, suggesting dysfunction of frontal limbic circuits. It has been suggested that hypofrontality in SZ leads to hyperactivity of subcortical dopaminergic systems. Lesions in the prefrontal cortex enhance the responsiveness of subcortical dopaminergic system to

pharmacological challenge and stress (Roberts et al, 1994, King et al, 1997). Augmentation of dopaminergic transmission in the frontal cortex, suppresses subcortical DA turnover and release.

The nucleus accumbens, which receives excitatory input from multiple frontal cortex and limbic structures, is also thought to be dysfunctional in patients with SZ. The nucleus accumbens is involved in both the glutamatergic and dopaminergic neurotransmission. The neuronal function in this area is altered by repetitive use of antipsychotics.

Deficits of sensory filtering in schizophrenics suggest involvement of the ventral pallidum and the thalamus in the disease.

The association areas of the parietal lobe integrate information coming from the visual, auditory and tactile sensory modalities, evaluate this and plan a response. The disruption of sensory integration is one of the earliest and most common symptoms of SZ. According to one study, "perceptual dysfunction is the most invariant feature of the early stage of SZ" and is found in almost two-thirds of patients (Cutting & Dunne, 1989). When the IPL is not functioning, the individual may be flooded with stimuli. Sensory data are difficult to be integrated into a coherent pattern. Given the difficulty in integrating sensory data, many individuals with SZ find it difficult to respond appropriately. This may lead to thought blocking or may produce loosening of associations. In fact, according to the literature, most aspects of thought disorder are probably explainable as defects in the sensory integration system of the IPL and other parts of the parietal cortex.

Additional examples of impaired sensory integration are neurological soft signs (NSS). Studies have shown that at least half of individuals with chronic SZ have such abnormalities (Torrey, 1980, Manschreck & Ames, 1984) and that they occur in individuals who have never been treated with antipsychotic medication (Keshavan et al, 2003). Such NSS have been linked to dysfunction of the parietal lobes especially to the supramarginal gyrus (Critchley, 1953, Lishman, 1978).

Disturbances in body image have been extensively described in individuals with SZ. Cutting (1989) reported disorders of body image in 45% of consecutive SZ admissions. The most

common manifestations were alterations in structure, shape, or weight. A common disturbance of body image in schizophrenics is right–left disorientation.

Individuals with SZ often experience disruptions in their sense of self, especially in the early stages of their illness (Sedman, 1970). Apart from depersonalization and derealization, one of the more dramatic disruptions of the sense of self is the feeling that “one's thoughts or actions are being influenced or replaced by those of an external agent (Spence et al, 1997). These are referred to as delusions of passivity and have been linked to the IPL dysfunction. Studies concluded that “passivity phenomena in SZ are associated with hyperactivity in the parietal cortex, perhaps lateralized to the right hemisphere” (Dankert et al, 2004) (see chapter 1, 3).

Whereas, at least in some studies, the performance of schizophrenic patients in DM tests is similar to that of patients with orbitofrontal lesions, other findings do not seem to correspond to the typical pattern observed in patients with that neurological lesion. One of the most prevalent study for a neurological connection is the one of Bechara et al (2005) who proposed that patients with OFPC lesion gave preference for higher risk decisions because they suffered of “myopia for the future,” i.e., they ignored previous experiences and did not adjust their behavior to a higher possibility of punishment inherent to this strategy, persisting in disadvantageous choices.

Existing studies reveal so far conflicting results regarding the association between DM and affected OFPC areas in SZ. Differences found and difficulties in replicating studies should consider many related variables, especially about selected samples, such as age of disease onset, diagnostic subtype of SZ, predominant symptoms, motor changes and the role of drugs on the neuronal systems involved in the selection of choices. The correlation of measurements obtained in tests assessing DM skills with the standard of psychosocial functioning is also important, since the latter is considered a reliable predictor of SZ prognosis. Most studies to date have not been able to establish a similarity as to performance pattern (at least in IGT) between schizophrenics and other victims of orbitofrontal neurological lesions, as those assessed in the first studies by Bechara et al (2005) and Damasio et al (1990, 1996). It is possible that differences are attributed not only to the clinical variables mentioned above, but also to anatomic and functional aspects that regulate the DM process and are not clearly understood

yet. On the one hand, if there is an involvement of non-cortical areas, such as the anterior cingulum and amygdala in the DM system, it is necessary to perform a more detailed screening of orbital cortical sectors (besides the OFPC) that account for the specific processing in different stages of the DM mechanism.

It is possible that current neuropsychological instruments are not specific to assess the complex processing of DM skills. Therefore, studies using more homogeneous samples and better defined methodological criteria as to clinical and demographic variables are needed, both to clarify the neurological basis and clinical repercussions of existing deficits, and also to define the role of current neuropsychological instruments.

A more detailed understanding of the mechanisms of emotional regulation and social judgment may have important consequences, especially in terms of clinical and psychosocial rehabilitation.

From all the tests used, manual and saccadic RT studies have shown the best reproducibility. From all the tests used in the evaluation of the schizophrenic disorder, no one has shown the consistency that has been noted in the slowing of RT. Experiments which started in the 60s showed schizophrenics to be slower than normal controls in both simple and complex RTs. The initial explanations with the principle of the “set index” (Shakow) and the use of the neuronal trace model (Zubin) [based on the assumption that facilitating and inhibitory neural traces had greater duration in schizophrenics] had not explained totally the phenomenon of RT slowness and the differences found between schizophrenics and controls. Payne and Caird’s studies on overinclusion and the Broadbent’s information processing model have not solved the problem either. Besides, it was not clear if in schizophrenics, slowness in RT was an attentional deficit or a more complicated cognitive phenomenon. It was not also clear the reason why RT appeared to be more related to the negative symptoms of SZ rather than the positive ones. It was also confusing that although RT slowness was consistently found in SZ, it was not specific for the disease, since it could be detected in various mental disorders.

Thus, RT slowness exists in SZ, but cannot exclude the diagnosis of another disorder. RT slowness is also found in depressives and manic depressives and in personality disorders with special schizotypal MMPI features. Although always present, RT slowness has not established

such diagnostic value to be used exclusively for SZ. Thus, RT has not fulfilled the initially expected role of a diagnostic or specifically prognostic laboratory test.

Later studies have mentioned the extreme variability of responses to be noticed in SZ to a higher degree compared to other psychiatric groups and to controls. But similarity of the variability distribution of RT responses has been also found in Attention Deficit Hyperactivity Disorders (ADHDs), complicating the facts and suggesting a common genetic defect in both disorders.

RT studies, although very promising 30 years ago, have run out of fashion in the last years and appear unable to give the diagnostic and prognostic key so desperately needed in the schizophrenias and their treatment follow-up (see also chapter 4).

The study of the saccades has added another dimension into the research of mental chronobiology. Since they reflect coordination of visual and cortical pathways, the integrity of the saccades and their RTs are important in health and in disease. As we have seen, SZ patients have significantly prolonged saccadic RTs equally prolonged to the left and right in almost all the experimental studies. Research has shown that this phenomenon is more pronounced in patients with negative symptoms of the disease. It is found that all elements of the saccadic system research (pursuit, motion etc) are impaired in schizophrenics. Besides, impaired saccades are evident in both simple and complex RT experiments.

The results of the Smyrnis et al (2009) study provide evidence in favor of the hypothesis that a specific difference in patients with SZ exists in the RT distribution, and this difference is present in a simple task in which there is no large psychomotor slowing. There is an increase in the mean saccadic RT for patients with SZ that remains significant after controlling for age differences. This increase, though, is found to be very small (5% of the mean for the control group). In contrast to this small increase in mean RT, there is a highly significant increase in the variability of RT in the patients that is confirmed in the significantly larger CV for this group (an increase of 35% compared with the CV for controls). This finding suggests a difference in RT distribution between these patients and the controls (confirmed by using the LATER model for RT distribution). The model parameters in the studies were significantly different for patients

than for controls. The difference in the shape of the RT distribution in SZ appears to be specifically linked to the performance deficits in these patients.

Various methods to calculate variability have been used such as the above mentioned model initially described by Carpenter & Williams (1995) which was applied in the studies of Smyrnis et al (2009) and Theleritis et al (2014). There is no doubt that such models study both the slowing of the manual and saccadic RTs, calculating the variability as well.

Vinogradov et al (1998) noticed increase in RT IIV in manual RT tasks, but Theleritis et al (2014) suggested that RT variability is also evident in the saccadic system as well.

By these studies, it appeared that the difference between schizophrenics and controls points towards a deregulation of the DM behavior, characterized by intermittent switching between highly predictable and highly unpredictable action.

The first RT experiments and those of saccadic movement ones, are extremely valuable.

Both manual RT and saccadic RT reflect cognitive function, especially related to attention, WM and DM processes. They are easily performed in the laboratory and although indirect, they relate to the level of the cognitive function of the individual. Although, they have not solved the problem if the slowness is due to disturbed attention or defective WM, in the future more elaborate experiments might illuminate this.

As we know, RTs are also found disturbed in relatives of schizophrenics and this may be helpful in current and future genetic studies of SZ.

The type of inheritance in SZ has not been solved and there is active research in isolating candidate genes with in vitro molecular techniques and the use of transgenic (knock-out and knock-in) animal models. The fact that relatives of SZ patients have both simple and complex manual RTs and saccadic RTs slowing compared to controls, points towards genetic transmission of the trait behavior in RT experiments. Not only the slowness in RTs but the variability of the performance compared to controls affects SZ patients' relatives, and reflects the above mentioned genetic risk. There is no doubt that this consistent finding is helpful in identifying relatives of schizophrenics who are at risk of developing the disease.

RT studies although invariably affected in SZ have not so far solved the etiology of the disease. This is because RTs in manual and saccadic experiments are slowed not only in SZ patients but

also in patients with depressive and bipolar illness. Schizotypal personalities show also RT slowness. Besides, the higher variability of RT compared to healthy controls, is not only found in schizophrenics but also in ADHD as well. Researchers have thought that there must be a common genetic component in both diseases.

Thus RT (both manual and saccadic) experiments appear that they could elucidate the SZ etiology only if they are linked with other clinical criteria and laboratory techniques.

DM is important in all humans since it helps reacting normally and appropriately to most situations. There is no doubt that, in SZ, abnormalities in hedonic capacity and other cognitive functions required for flexible control of behavior occur.

RT studies in manual and saccadic experiments reflect the DM abnormalities in SZ and are helpful markers of the DM impairment of these patients. Especially, the RT IIV reflects that there is also IIV in the DM process in these patients. The variability in RT points towards a deregulation of the DM behavior, characterized by intermittent switching between highly predictable and highly unpredictable action.

Existing studies reveal so far conflicting results regarding the association between DM and affected OFPC areas in SZ. Differences found and difficulties in replicating studies should consider many related variables, especially about selected samples, such as age of disease onset, diagnostic subtype of SZ, predominant symptoms, motor changes and the role of drugs on the neuronal systems involved in the selection of choices. The correlation of measurements obtained in tests assessing DM skills with the standard of psychosocial functioning is also important, since the latter is considered a reliable predictor of SZ prognosis.

Most studies to date have not been able to establish a similarity as to the performance pattern (at least in IGT) between schizophrenics and other victims of orbitofrontal neurological victims, assessed in the first studies by Bechara et al (2005) and Damasio et al (1996). It is possible that those differences are attributed not only to the clinical variables mentioned above, but also to anatomic and functional aspects that regulate the DM process and are not clearly understood yet. If, on the one hand, there is an involvement of other non-cortical areas, such as the anterior cingulum and amygdala in the DM system, it is necessary to perform a more detailed screening of orbital cortical areas (besides the OFPC) that account for the specific processing

and in different stages of the DM mechanism. It is possible that current neuropsychological instruments are not specific to assess the complex processing of DM skills. Studies using more homogeneous samples and better defined methodological criteria as to clinical and demographic variables are needed, both to clarify the neurological basis and clinical repercussions of existing deficits, and also to define the role of current neuropsychological instruments. A more detailed understanding of the mechanisms of emotional regulation and social judgment may have important consequences, especially in terms of clinical and psychosocial rehabilitation.

Thus, it appears that due to the complex factors regulating the DM processes, the RT studies are not enough if they are not linked with other types of research (genetic, neuroimaging, neuropsychological tests, clinical evaluations etc).

The specificity of the RT experiments (even with the best possible arrangements and the best possible analytical models) is problematic. This is especially due to the fact that similar speeds and variabilities are also found in other mental pathologies such as ADHD. Thus, the specificity of the method is not guaranteed. The above mentioned and well known problem of affected relatives and schizotypal personalities is also pervasively present even in the best set-ups. Even monogygotic twin studies cannot solve the problem without: 1) perfect clinical and diagnostic criteria, 2) appropriate molecular identification of the genetics of the disease 3) final decision if SZ is one or more than one disorders.

There is no doubt that SZ has a major genetic and hereditary component (figures 6.1 και 6.2).

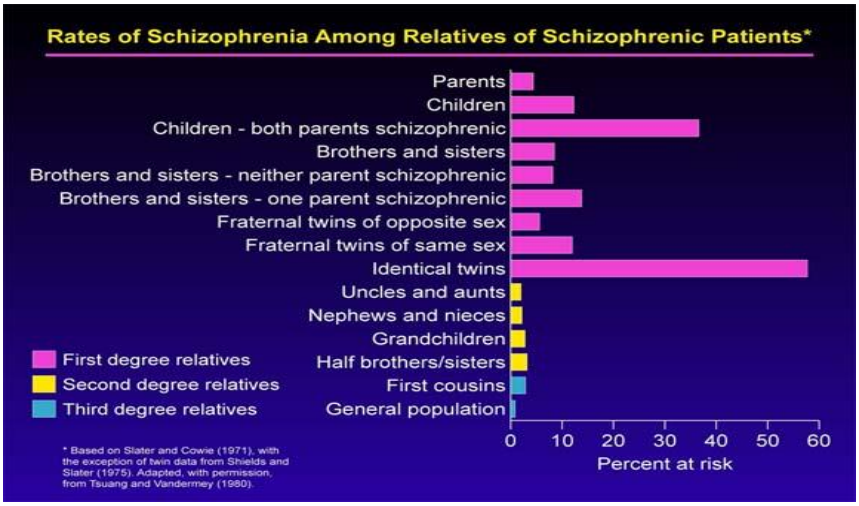

Fig. 6.1 Incidence of SZ in relatives of the patients (source internet)

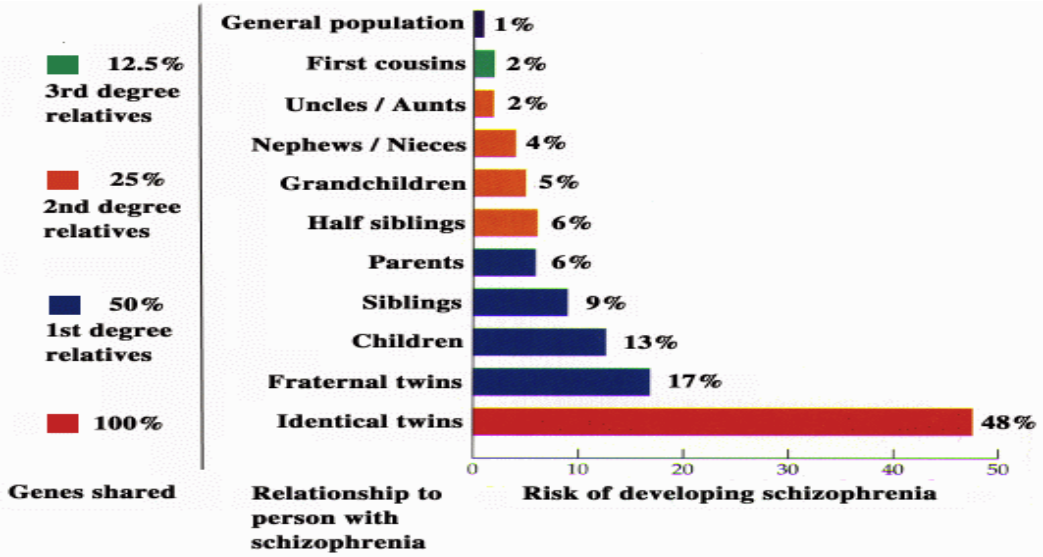

Fig. 6.2 Incidence of SZ in the patients' relatives. Comparisons with the general population (source internet)

Looking at the incidence of the disorder in the general population the need for proper genetic studies is obvious.

SZ appears to be a group of heritable disorders caused by separate genotypic networks that are associated with several distinct clinical syndromes, and not just one single disease. The current research findings may lead to better diagnosis and improved treatments personalized for each patient with the disorder. What is suggested is that there is not one SZ, there are SZs, and that there are several subtypes. At least 8 different classes of SZ were identified (and of course there may be more) that have different symptoms and different severity and are caused by separate clusters of genes that act together (Arnedo et al, 2015).

The finding that SZ is not a single entity but a variety of SZ subtypes has important implications for research and treatment of this illness.

One of the problems right now is that patients with SZ may receive the same diagnosis and yet share few symptoms in common. These symptoms can vary in terms of severity and response to treatment. Zwir and his colleagues (2014) matched precise DNA variations in people with and without SZ to symptoms in individual patients. In all, they analyzed nearly 700,000 sites within the genome where a single unit of DNA is changed, often referred to as a single nucleotide polymorphism (SNP). They looked at SNPs in 4200 people with SZ and 3800 healthy control

individuals, learning how individual genetic variations interacted with each other to produce the illness. In some patients with hallucinations or delusions, the researchers matched distinct genetic features to patients' symptoms, demonstrating that specific genetic variations interacted to create a 95% certainty of SZ. In another group, they found that disorganized speech and behavior were specifically associated with a set of DNA variations that carried a 100% risk for SZ. In all, they identified 42 clusters of genetic variations that increased the risk for SZ. The work which was one of the Psychiatrics Genetics Consortium, described 108 specific genetic associations with SZ. It had the largest sample of patients, over 40,000, ever studied, and it was found that the mechanisms of heritability and transmission of illness are far more complex than we had originally expected (Arnedo et al, 2015). Thus, if SZ is so complicated to diagnose or if it is more than one disease, then it is not strange if the experimental studies with RT (manual or saccadic) show such variability and do not seem to give full explanation.

Full explanation on the role of RT in DM processes will be achieved only if genetic subtypes are isolated with genetic and clinical studies. There is no possibility that RT (manual or saccadic) can be helpful if the groups of the disease are not properly homogenized. For this to be achieved, long term studies and improvement of the applications of the genetic laboratory techniques are required.

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