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Directions in Research into Response Selection Slowing in Schizophrenia

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1. Introduction

People with schizophrenia experience many types of symptoms and a particularly difficult type are cognitive. Cognitive deficits are relevant to prognosis (Green, 1996; Green, Kern, Braff & Mintz, 2000) and improvement in cognitive skills may produce gains in emotional, physical, social and vocational adaptation (Matza et al., 2006). Response selection slowing is perhaps the most straightforward way to show a cognitive deficit in schizophrenia and has a long history in schizophrenia research. Response selection plays a role in virtually any task that requires a motor response; thus it is important to understand it fully in the context of schizophrenia to allow appropriate and valid interpretation of other cognitive tasks. Adding to its importance is that response selection may also be an endophenotype of schizophrenia. This paper will summarize recent results in neuroimaging of response selection in schizophrenia. As well, the best test of our understanding of the deficit in response selection slowing in schizophrenia will be through simulation, so progress in computational models using neural networks will also be examined.

This chapter will begin by summarizing the long history of research in response selection slowing in schizophrenia. It will then proceed with a description of various neuroimaging techniques that are used in the studies that will be discussed. Following that, landmark studies in response selection in healthy people will be summarized followed by the discussion of studies in response selection in schizophrenia. The next-to-last section will highlight some research in simulation that show promise in modeling the differences in response selection in people with schizophrenia before ending with a concluding paragraph.

2. History of response selection slowing in schizophrenia

The prototypical response selection task is choice reaction time (RT) with RT being the measured variable. Whereas simple RT tasks require the same response to any stimulus, choice RT requires a decision among a choice of responses dependent on the stimulus. The modality (auditory, visual, tactile) makes a difference in the RT, with auditory being faster than visual (Naito et al., 2000), as well as stimulus-response compatibility, where responses that are more compatible are faster, and the preparatory interval (period of time before the

stimulus) where a longer RT generally results from a longer preparatory interval. Studies of response selection almost invariably require a series of trials, and the order of trials and mix (regular/irregular) of preparatory intervals can lead to effects on reaction times which have been exploited in various ways. Variables of interest include median RT, measures of the distribution of reaction times (e.g. interquartile range), mistakes (incorrect response to stimulus), errors of omission (no response to a stimulus) and errors of commission (responding without a stimulus).

A slowing in visual or auditory RT was demonstrated in early schizophrenia research (for a review, see Wells & Kelley, 1922). Investigation of response selection in schizophrenia was extensive through the middle decades of the 20th century (see Nuechterlein (1977), for a review), and many versions of RT tasks were developed in pursuit of an objective test for schizophrenia (e.g. Huston, Shakow & Riggs, 1937); however, the results were never specific enough to be used with confidence for individuals. A strength of these early studies is that when they were completed, neuroleptic and antipsychotic drugs were not available, so patients participating in these studies were drug-free. However, the diagnosis of schizophrenia has evolved over time. The Diagnostic and Statistical Manual of Mental Disorders (DSM) wasn't introduced until 1952 and dramatically revised and accepted in the 1980s, so modern studies use a somewhat different sample.

Similar to measures of more complex cognitive functions, the response selection deficits in schizophrenia are related to poor outcome. Studies by Zahn and Carpenter and Cancro et al. in the 1970s correlated longer RT with increased hospitalization for schizophrenia (Zahn & Carpenter, 1978; Cancro, Sutton, Kerr & Sugarman, 1971). Silverstein et al. included auditory simple RT in a study involving several other common neurocognitive tests (Silverstein, Schenkel, Valone & Nuernberger, 1998). They found that the presence of an error of commission predicted reduced performance at the end of training of individuals with schizophrenia.

More recently, Ngan and Liddle studied reaction times in populations with schizophrenia and found (negative) correlation between disorganization and negative symptoms with simple RT in persistent illness populations, and (negative) correlation between disorganization symptoms with choice RT in the same population (Ngan & Liddle, 2000). Another recent study (Pellizzer & Stephane, 2007) found that mean RT in a 2-choice RT task did not predict mean reaction time (RT) in a 4-choice RT task in people with schizophrenia, whereas as it did for healthy controls. They suggested that this indicates that the slowing in schizophrenia from increased choices is a different process from the slowing in healthy persons.

Response selection slowing in schizophrenia could also be important due to its heritability. Reaction time has been shown to be one of the most heritable cognitive tasks. A twin study looking at both simple and choice RT found 64% and 62% heritability respectively at 16 years of age (Rijsdijk, Vernon & Boomsma, 1998). Another twin study also found 64% heritability for choice RT (Wright et al., 2001). This is higher than working memory tasks (below 50% in Wright et al., 2001). As well, RT has been shown to be weakly but reliably correlated with IQ, with estimates of between -0.2 and -0.4 (Rijsdijk et al., 1998; Wright et al., 2001).

The heritability of response selection would be important if we can show a difference between people with schizophrenia, first-degree relatives of schizophrenia and healthy

volunteers using neuroimaging. Schizophrenia has a sizable genetic loading, but there has been limited progress in identifying suspect genes for schizophrenia. One reason argued for limited progress in genetic analysis is that schizophrenia may not be a single disease (e.g. Hallmeyer et al., 2005). Subsequently, active research programs are on to identify endophenotypes (Braff, 2007). Where phenotypes are the outward, visible expression of the genotype, endophenotypes are an intermediate expression of the genotype that must be measured rather than being obviously visible. Endophenotypes are regarded as closer to the genetic variation than the phenotype, and thus endophenotypes of schizophrenia may be more amenable to genetic analysis than the phenotype. Endophenotypes should show measurable differences between people with schizophrenia and healthy volunteers, as well as being heritable. Therefore, response selection is an excellent candidate for an endophenotype as it is strongly heritable and is measurably different.

It is important to point out that although choice RT seems like a simple paradigm, it in fact involves many complications because of the serial presentation for neuroimaging. It seems that there are many unconscious operations that may be involved, as well as attention, and the many different details of paradigms can affect these. Some of these unconscious operations must include interval timing and recognizing patterns. For example, the fMRI study by Praamstra et al. (2006) investigates interval timing using a serial choice RT task (Praamstra et al., 2006), and several studies in schizophrenia have examined procedural learning with a serial choice RT paradigm (Zedkova et al., 2006; Woodward et al., 2007). These complications can introduce difficulties in interpreting results, especially since, as we have seen with various ACC activations, these activations can happen at different times post-stimulus and may be involved in different processes of the task.

3. Neuroimaging studies of response selection

Research into response selection slowing has been revived by advances in neuroimaging. Neuroimaging offers possibilities to identify where and when the deficits in schizophrenia arise in the response selection process. A first step is to understand the process in healthy people. Neuroimaging studies of response selection have been reported using the full suite of imaging techniques including PET (e.g. Iacoboni et al., 1996; Naito et al., 2000), EEG (e.g. Mulert et al., 2003), fMRI (Jiang and Kanwisher, 2003; Winterer et al., 2002) and MEG (Thoma et al., 2006).

3.1 Neuroimaging techniques

There have been many neuroimaging techniques employed in the study of response selection. To appreciate the literature, an understanding of these techniques is important. The techniques are described briefly below.

Electroencephalography (EEG) was first used on humans by Hans Berger in 1924. It measures electrical potentials on the scalp using a number of electrodes, e.g. International 10-20 system for clinical use has 19 electrodes plus a reference; research systems typically have more electrodes. The potentials are created by changing ionic current flows in populations of neurons (hundreds of thousands to millions) and are in the range of plus and minus 100 μV. Each electrode records the potential across time at a high resolution (milliseconds). EEG is often used to record event-related potentials (ERPs) by repeating

events many times. ERPs are created from raw EEG signals by cutting each session into individual events, synchronizing the events according to an external signal (either stimulus or response) and averaging them together. This eliminates noise and allows the detection of peaks and valleys that line up with the stimulus or the response, depending on which is chosen as the reference (stimulus-locked or response-locked). The transmission of the electric potentials through the head is complicated and difficult to model, and this limits the ability to determine the spatial source of the EEG signals. EEG equipment is cheap compared to the other techniques described and can be done on almost anyone.

Magnetoencephalography (MEG) resembles EEG, and can be analyzed using the same methods, but measures magnetic potentials around the head instead of electrical potentials. Instead of electrodes contacting the scalp, it uses magnetic potentiometers and gradiometers that do not have to contact the scalp. The magnetic fields are very, very small (pT) and are easily overwhelmed by environmental noise such as cars passing by on the street, or elevators moving within the building, so MEG machines must be kept in very well shielded rooms. The potentiometers are based on SQUIDS – supercooled quantum interference devices. The magnetic potentials transmit through the head in a much more well-defined manner than the electrical potentials and many more potentiometers may be used, so MEG provides the potential for spatial resolution of sources to within 5 mm as well as millisecond time resolution like EEG (although the ability of MEG to detect and spatialize signals from deep within the brain is in question). MEG equipment is quite expensive, but its advantages and the fact that almost anyone can be scanned with MEG make it a desirable neuroimaging technique.

Functional magnetic resonance imaging (fMRI) uses magnetic resonance imaging sequences that are sensitized to blood flow in the brain. Blood flows more to active areas of the brain, to maintain energy to run the neural electrical interactions and biochemical reactions. The most common technique is BOLD (blood oxygen level dependent), demonstrated by Ogawa in 1990 (Ogawa et al., 1990). Blood oxygen level increases with neural activity as oxygen-laden blood rushes in to areas of high activity. Deoxygenated blood has a different magnetic susceptibility than oxygenated blood, which creates small changes in the local magnetic environment that can be measured with the magnetic resonance imaging scanner. As the changes are small, the activation is detected statistically, usually by comparing the measured signal with the expected signal under a general linear model framework. Cognitive tasks are analyzed using block designs as used in PET studies (fMRI's predecessor), or with event-related designs that are more similar to EEG or MEG paradigms. As the measurement of neural activity is indirect – through blood flow changes and then magnetic environment changes – physiological changes unrelated to cognitive activity can also affect the signal measured by fMRI. The hemodynamic response is the shape of the measured response to instantaneous neural activity. The shape of the hemodynamic response has been measured in various specific situations and brain areas and found to be roughly consistent between people and brain areas, and to add up roughly linearly to a sequence of events. The hemodynamic response has a delay of a few seconds, a rise up to a plateau and then a drop back to equilibrium. In all, the hemodynamic response can last 20 seconds before return to equilibrium in response to a brief neural event. The shape is often assumed in the analysis with only amplitude varied, though some analysis techniques do

not depend on knowledge of this shape. fMRI is able to provide spatial localization to within a few mm, but has poor time resolution as a result of the hemodynamic response, although clever methods have been developed to measure events to a finer time resolution.

Positron emission tomography (PET) uses radioactive tracers that are injected into the subjects. The radioactive tracers emit positrons that give off gamma rays (photons) that can be detected on the outside of the machine when the positrons interact with matter. The gamma rays travel in approximately opposite directions after they are created and the machine notes gamma rays that arrive on opposite sides of the detector at approximately the same time. The machine can then trace the pair of gamma rays back to identify where they originated. In a session, many of these events must be counted and traced back to determine the levels of radioactivity in the body. Different radiotracers can be injected that will bind to different functional processes in the body, allowing many different types of functions to be imaged. The most common tracer in neuroimaging is fluorodeoxyglucose (FDG), a sugar that performs the same functions biologically as glucose. In the brain, FDG is taken up more by active cells, leading to increased radioactivity in active parts of the brain. The measurement is referred to as regional cerebral blood flow (rCBF). However, the use of ionizing radiation limits performing multiple scans on the same individual. As well, the radioisotopes take some time to reach their destination in the body (~ 1 hour with FDG), and time to count, limiting the kinds of cognitive tasks that can studied. PET was developed before fMRI and was used for cognitive studies in the 80s and 90s, but is not widely used for these purposes anymore.

3.2 Neuroimaging studies of response selection in healthy controls

The first neuroimaging applications to response selection used PET (Taylor et al., 1994; Iacoboni et al., 1996). Taylor's study found that increased rCBF in the cingulate gyrus correlated with faster reaction time. Iacoboni used a choice RT task with a visual stimulus with button response from either hand (stimulus-response compatible) or reversed response (incompatible) and found increased rCBF in bilateral superior parietal lobules with the incompatible task. Another study by Naito et al. (2000) looked at simple RT to stimuli in various modalities in healthy volunteers using positron emission tomography (PET) (Naito et al., 2000). They found that in all modalities, the reaction time was negatively correlated with activation in a part of the anterior cingulate cortex (ACC) (See Figure 1).

Mulert and colleagues looked at choice RT to an auditory stimulus using electroencephalography (EEG) and low resolution electromagnetic tomography (LORETA – a method to determine spatial location of electrical sources) and found a similar relation between current density in ACC, RT, and error rate (Mulert et al., 2003). Mulert and colleagues used the same paradigm and analysis to compare people with schizophrenia to healthy controls (Mulert et al., 2001) and first-episode schizophrenia (Gallinat et al., 2002). These results will be highlighted in the next section.

fMRI has frequently been used to investigate response selection. In some cases, a choice RT task is used as a control and such was the case with Jansma and colleagues (2000). Jansma's study, which was intended to look at learning, included choice RT to a visual stimulus in

healthy volunteers and found ACC activity among other activations, although they did not attempt to correlate RT to degree of ACC activation (Jansma et al., 2000).

Another study examined choice RT with a visual stimulus in healthy volunteers using event-related fMRI (Winterer et al., 2002) and found the same negative correlation between activity in ACC and RT (see Figure 1) as had been found by their group earlier in auditory choice RT using EEG (Mulert et al., 2001).

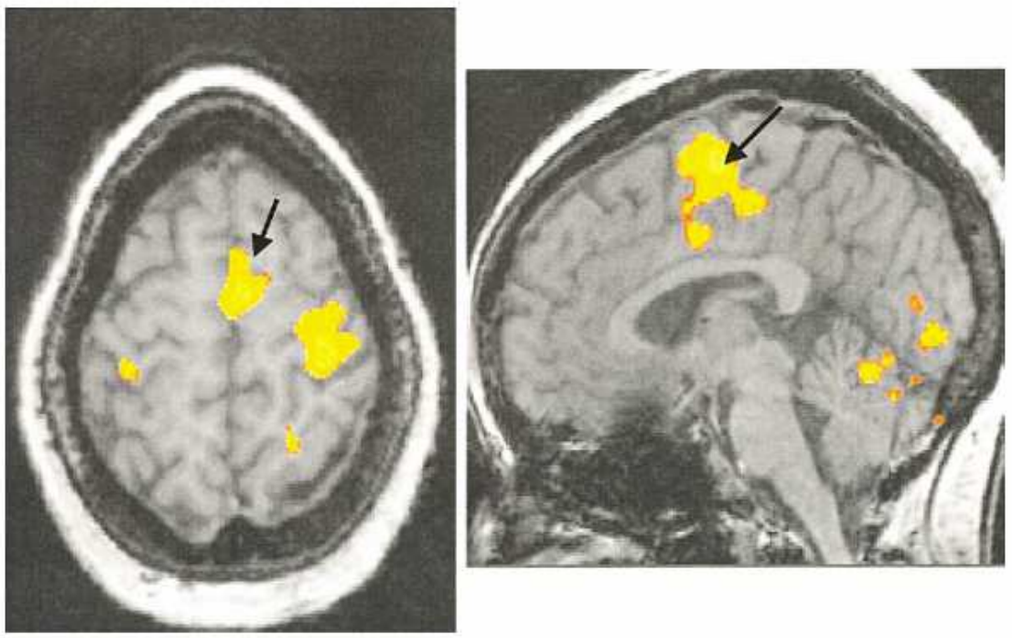

Fig. 1. Results from Winterer et al. (2001) showing activation in ACC/SMA from event-related visual 2-choice reaction time task. Reprinted with permission.

The fact that ACC activation in a response selection task in healthy populations has been consistently found by different researchers using different imaging techniques and different paradigms makes it a robust finding. There is a conflict about ACC function between theories of selection-for-action (Posner & DiGirolamo, 1994) and conflict monitoring (Carter et al., 2000), but these differing roles may be resolved by findings that ACC is a heterogeneous functional area (Swick & Jovanovic, 2002; Vogt et al., 1992; Picard & Strick 1996), and that ACC activity is seen at different times during the response, namely early (~ 130 ms post-stimulus) (Mulert et al., 2001) and late (~240 ms, 360 ms, 390 ms and 414 ms post-stimulus) (Winterer et al., 2001).

Another task that provides some insight into this controversy is the Attention Network Task (ANT) developed by Fan (2001) to investigate different aspects of attention: namely alerting, orienting and executing. An event-related fMRI study of the ANT task identified ACC activity only during the executive aspect (Fan et al., 2005). The study compared results from one aspect with results from another, so any activation that is common in the aspects of the ANT task is not identified as a component of a particular aspect. Thus, the activation during the executive phase is most likely the late activation of ACC connected

with performance (conflict) monitoring, and early activation of ACC in the response selection is not identified.

Several other fMRI studies have focused on various aspects of response selection in healthy populations. Dassonville et al. (2001) looked at the effect of stimulus-response compatibility at 2 levels – set-level and element-level (Dassonville et al., 2001). Set-level changes the set of stimulus and response characteristics (using spatial versus symbolic stimulus in this experiment), whereas element level changes only the mapping between stimulus and response (such as reversing responses in the Iacoboni et al. (1996) task, or in the Dassonville experiment, direct or counter-clockwise mapping). In this study, 4 conditions were compared in 11 regions-of-interest. Element-level changes produced more activation in pre-supplementary motor area, dorsal and ventral premotor areas and parietal areas, and activation was lateralized to the right hemisphere. Set-level changes produced more activation in the same areas plus inferior frontal gyri, anterior cingulate, cingulate motor areas and superior temporal lobe, and activations were lateralized to the left hemisphere (see Figure 2). These results apply to changes in stimulus-response compatibility of the tasks, and the differences between the 3 sets in Figure 2 show the effect of set, element, and set and element level changes.

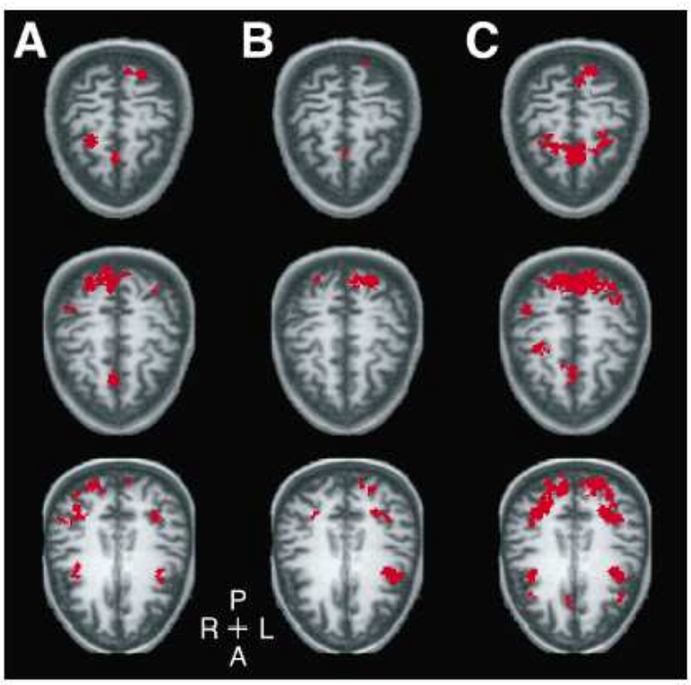

Fig. 2. Spatially congruent activation at three different anatomic levels in the (A) spatial/ccw, (B) symbolic/direct, and (C) symbolic/ccw tasks (A-B: set and element; B-C: element; A-C: set level changes). From Dassonville et al, 2001. Reprinted with permission.

A set of studies of response selection investigated commonality of functional activations with domain of stimulus (auditory, somatosensory, visual) and with perceptual processes (Jiang and Kanwisher, 2003; Jiang and Kanwisher, 2003a; Schumacher et al., 2003). The first study used a 4-choice perceptual decision task in visual, auditory and verbal domains to show common neural substrates of response selection with stimulus modality. These were found across bilateral parietal and frontal regions. The second study compared perception and response selection tasks and found common activation between them in all the ROIs investigated, a contradictory finding to the behavioural finding that response selection is a unitary process subject to dual task interference whereas perceptual processing can carry on in parallel. Schumacher and colleagues investigated the commonality of response selection between spatial and nonspatial stimuli and found a dissociation of areas. The conflicts between these findings were discussed by Schumacher and Jiang (Schumacher & Jiang, 2003), and although they can provide an explanation for the seemingly divergent results, the process provides an interesting lesson in the limitations of interpreting results from a single study; namely, to be careful how generally you interpret the results from a single task.

An interesting recent paper investigated trial-by-trial variation of RT using fMRI (Yarkoni et al., 2010). The authors describe the analysis of a set of results combined from several different studies of different tasks. All of the tasks were significantly more complex than choice RT with significantly longer reaction times. However, even with the use of different tasks, a set of areas was identified whose activity varied with the reaction time (time-on-task), and another set whose delay in activity correlated with reaction time (temporal shift). Areas showing time-on-task correlation would seem to be directly involved in the processes that vary in length to create variable RTs, whereas areas showing temporal shift would be areas that are activated following the time-on-task areas. An enormous set of regions was identified with the different effects roughly spatially-segregated. The time-on-task areas included frontoparietal and thalamic, whereas temporal shift were strongest in somatomotor, visual, cerebellar and posterior midline cortical regions. These results help to show the temporal sequence of activation of areas, and which areas are most responsible for varying RT. That this temporal sequence can be seen in fMRI results is very significant and provides motivation to attempt this type of breakdown in studies of schizophrenia. We will see alternate ways to approach this temporal sequence issue using EEG and MEG in the next section.

Choice RT has even been investigated in connection with white matter pathways supporting visuospatial attention (Tuch et al., 2005). This study used diffusion tensor imaging, a technique of MRI, to measure the fractional anisotropy (FA - a measure of orientation coherence of water self-diffusion indicating health of white matter pathways) of white matter pathways in the brain and found a positive correlation between FA and choice RT in several different pathways associated with visual processing. It would be very interesting to perform such a study in people with schizophrenia to look for a similar correlation between FA and choice RT.

A MEG study of response selection has also been reported (Thoma et al., 2006). The study concentrated on the timing of various identifiable steps in the response selection process for simple and 2-choice RT tasks. These were visual - identified by a magnetic dipole in contralateral calcarine cortex; motor – identified by a magnetic dipole in pre-central gyrus immediately prior to the response; and somatosensory – identified by a magnetic dipole in

post-central gyrus immediately following the response (see Figure 3). The behavioural response occurred between the motor and somatosensory dipoles. Visual-Motor Integration (VMI) time was calculated as the difference between the visual dipole and the motor dipole.

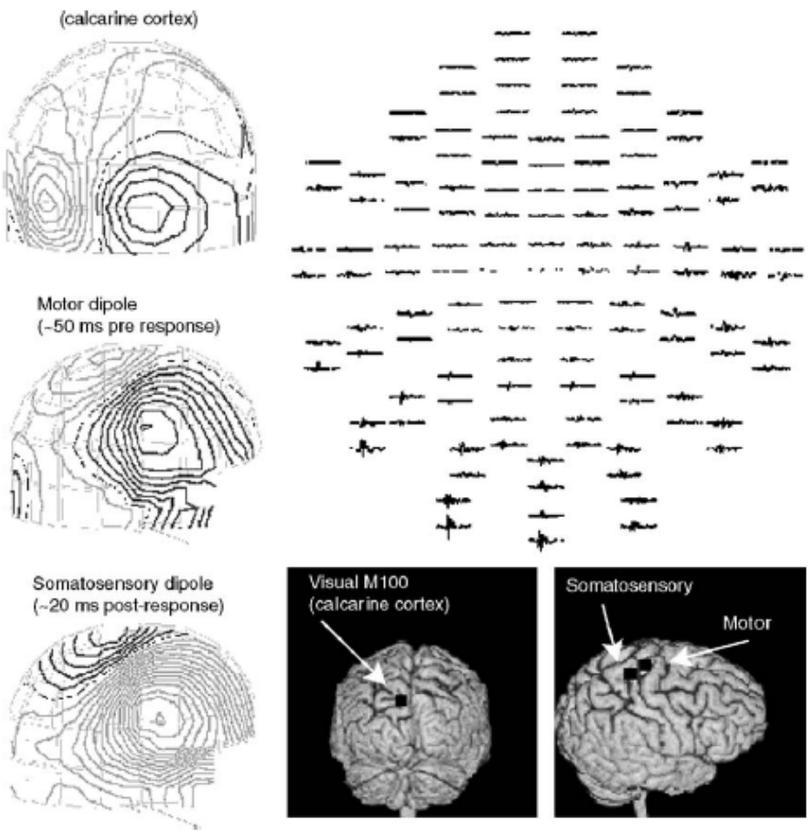

Fig. 3. A right-visual hemifield stimulus presentation with left hand response results in MEG data as shown. This figure contains a field pattern, contour map for each dipole, and localization for each of visual, motor, and somatosensory dipoles. From Thoma et al, 2006. Reprinted with permission.

The visual stimulus was a circular checkerboard presented briefly (50 ms) in left or right hemisphere and four conditions were used – right-only response, left-only, ipsilateral response and contralateral response. MEG and RT data were correlated with scores on Raven's Advanced Progressive Matrices and fluctuating asymmetry, a measure of developmental instability. Significant correlations included a negative correlation between the VMI time and RAPM score (smaller VMI time with higher score) and a positive correlation between the visual response latency and RAPM score. The results show that the varying reaction times arise primarily between the visual and motor dipoles. Although this is quite a broad breakdown of the temporal sequence and a finer scale would be useful, similar studies in people with schizophrenia would be useful to identify where and when neural processes are different from healthy people.

Another neuroimaging technique that is relevant in the context of animal studies is single neuron recording. Animals such as monkeys can be trained to perform various forms of

choice RT tasks, and modern electrodes and surgical implantation techniques allows recording from conscious animals while they perform these tasks. The advantage of such recordings is the specificity and time resolution. Prior knowledge is used to determine likely places to implant the electrodes to obtain a response for the particular cognitive task being investigated. In recent years, single-cell recording of awake monkeys performing a visual discrimination task has identified areas that may be involved in the decisions (Roitman & Schadlen, 2002; Schall, 2002). By correlating the rate of rise of activity in implanted areas with the behavioural decision time, areas in the middle temporal lobe, lateral intraparietal area in extrastriate cortex, the frontal eye field and superior colliculus have been identified. These results were specific to the task requiring a visual response (saccade) as well as a visual stimulus, so involvement of areas such as frontal eye field and superior colliculus is probably not relevant to a motor response, but middle temporal lobe and laterial intraparietal area could be more generally involved for any response.

In summary, response selection has been investigated for some time in healthy populations to aid in a better understanding of basic cognitive functioning. More sophisticated neuroimaging techniques and methodologies have allowed further refinement of the spatial and temporal sequencing of this key cognitive function., but there are unresolved questions about the temporal sequencing of functional areas involved in response selection.

3.3 Neuroimaging studies of response selection in schizophrenia

Several neuroimaging studies of response selection have looked specifically at individuals with schizophrenia (Mulert et al., 2001; Gallinat et al., 2002; Woodward et al., 2009; McAllindon et al., 2009; Luck et al., 2006; Luck et al., 2009). Other studies have used simple RT as a paradigm in people with schizophrenia (Barch et al., 2003).

The studies by Mulert and Gallinat were similar to each other and used EEG and an auditory choice RT paradigm. Mulert studied a population with chronic schizophrenia and Gallinat looked at first-episode psychosis. Both studies reached a similar conclusion that an area roughly identified as anterior cingulate cortex showed a lower current density in performing the task in people with schizophrenia (See Figures 4 and 5). It should be noted that these EEG studies concentrated on a time about 100 ms post-stimulus that may be a different function (selection-for-action) than activation in the ACC that has been identified at later times (conflict monitoring) (Winterer et al., 2002).

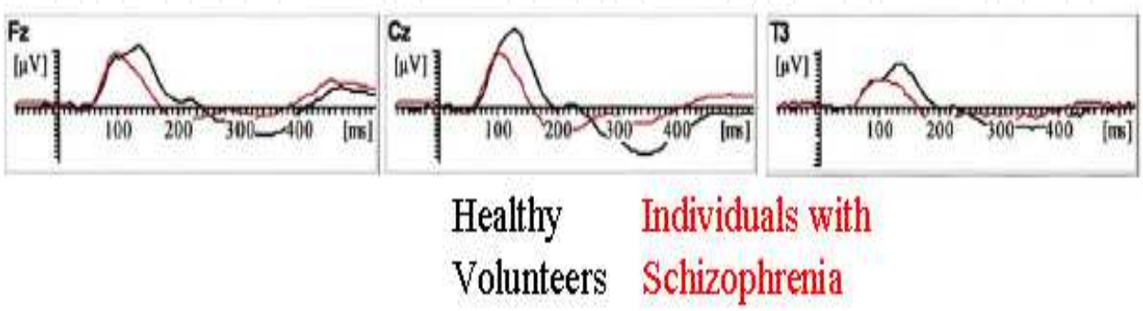

Fig. 4. Selected ERP grand averages comparing healthy volunteers (black) to individuals with schizophrenia (red). From Mulert et al., 2001. (Grand Average is average of all subjects' ERPs.) Reprinted with permission.

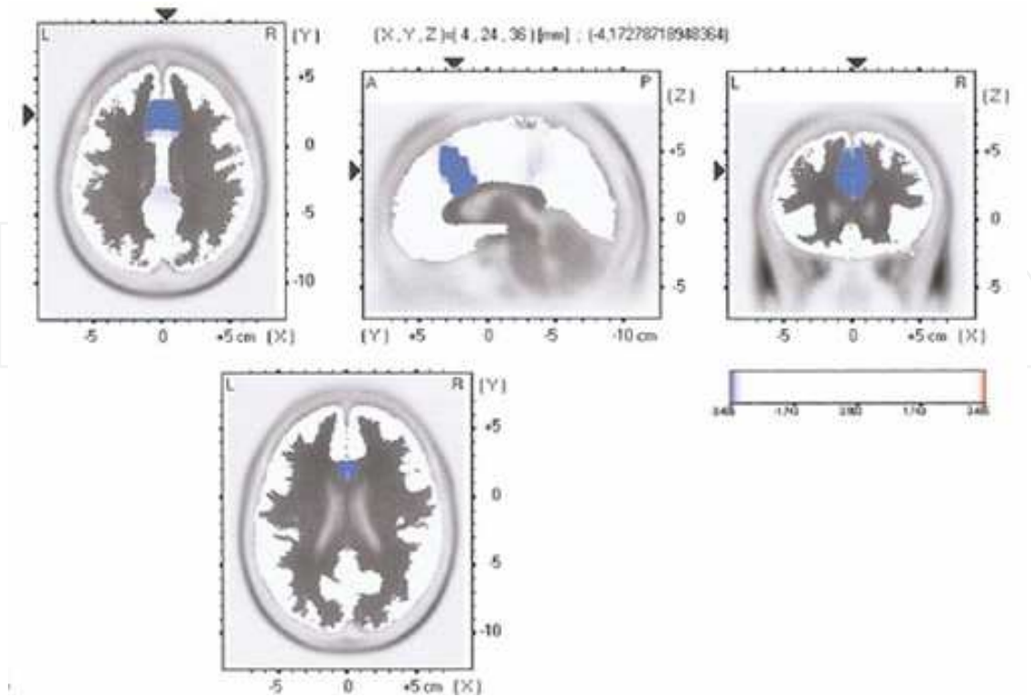

Fig. 5. LORETA results from ERP recordings showing reduction in current amplitude during auditory choice reaction time task. From Gallinat et al., 2002. Reprinted with permission.

Mulert proceeded to perform 2 further studies of response selection slowing to help explain the earlier findings. One possible explanation for the function of this early, ACC-related task is effort or degree of engagement with the task. This theory was investigated by Mulert et al. (2005) who were able to correlate ACC activation and RT with the self-reported effort on the task (Mulert et al., 2005) (See Figures 6 and 7). This is a very interesting explanation since a major confound with cognitive tasks on individuals with schizophrenia is whether the results are biased by their involvement with the task. The early ACC activity may actually be a neural sign of the degree of engagement in a task by individuals with schizophrenia (and healthy volunteers).

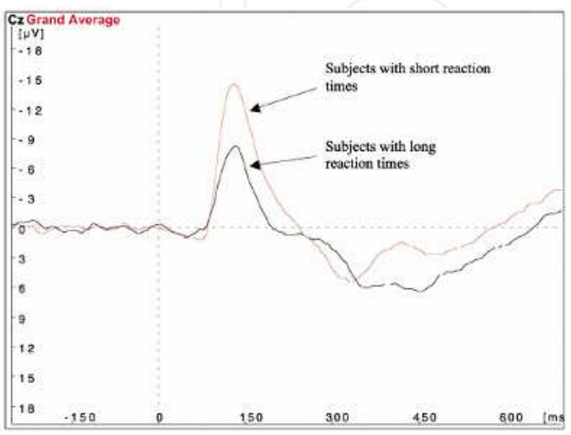

Fig. 6. Grand Average at Cz electrode for long and short reaction times. From Mulert et al., 2003. Reprinted with permission.

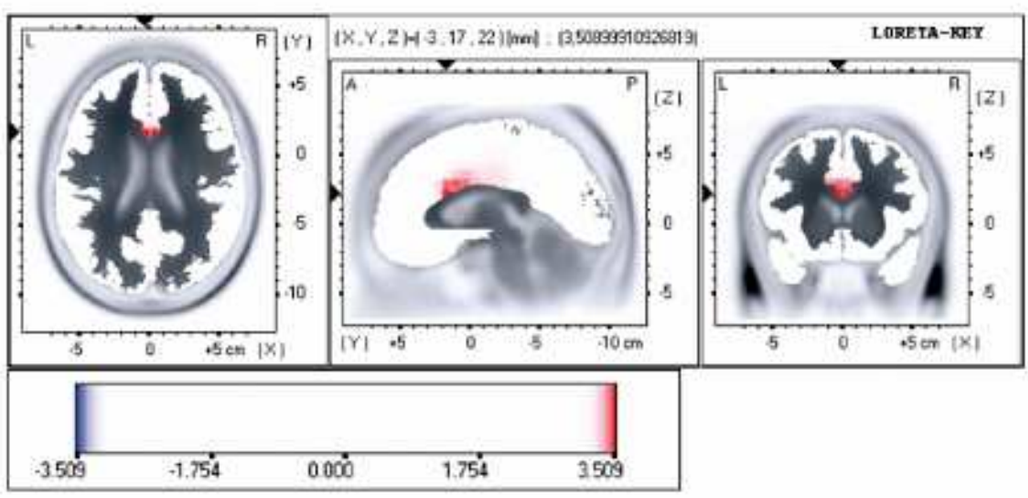

Fig. 7. LORETA results from ERP testing identifying area of increased current amplitude for short reaction times compared to long reaction times. From Mulert et al., 2003. Reprinted with permission.

Another of Mulert's studies (Mulert et al., 2003) (mentioned earlier) investigated the relation of error rate to RT and ACC activity, as the ACC has been suggested to be involved in performance monitoring (MacDonald et al., 2000). The results from this study found the expected relation between RT, error rate and current density in ACC. However, the timing of the tasks is important. The localization of performance monitoring functions to ACC has been shown by fMRI, which contains no time information. It would fit the evidence if the performance monitoring function of the ACC comes later than the response selection function, so that what we are seeing in response selection tasks is the early activation of ACC. Support for this idea also comes from neuroimaging of the ANT task, as discussed previously.

Luck has performed a series of EEG studies in an effort to localise when the cognitive deficit in response selection in people with schizophrenia occurs (Luck et al., 2006; Luck et al., 2009). The first of this series is reported in Luck et al. (2006), Experiment 1 and tries to identify if there is a deficit in speed of allocation of attention. It used the N2pc component as a marker of the time when perceptual processing becomes focused on a target item. The N2pc can be isolated laterally allowing it to be identified in a difference waveform. The task was to identify the side of a gap in a red or green square target in a sea of white squares against a dark grey background. In this, it was more complicated than a typical measure of response selection. The results showed a slowing of RT of about 150 ms in people with schizophrenia with a mean 800 ms RT for controls, but showed no difference in onset latency of the N2pc (see Figure 8). Both groups showed about 40 ms faster RT to red targets and about 50 ms less onset latency to red targets in the N2pc. Thus, there was no difference in speed of attention allocation.

The second experiment was a behavioural experiment that provided support for the interpretation of the first experiment. It used a variant of the Posner spatial cueing task that allowed a comparison of a behavioural measure of speed of allocation of attention between control and schizophrenia samples. The task was to report the identity of the letter in a circle

of letters that is indicated by a marker before all letters are masked. By varying the time between the marker and the mask, the time to shift attention can be measured. Although there was a small increase in speed of attention of the schizophrenia sample of 102 ms versus 83 ms for controls that was marginally significant (p=0.053), this appeared to be entirely due to 4 outliers in the schizophrenia group. Luck et al. argue that these outliers are unrepresentative of the schizophrenia group as a whole and should be excluded. This behavioural measure would then agree with the neurimaging results showing no difference in speed of allocation of attention.

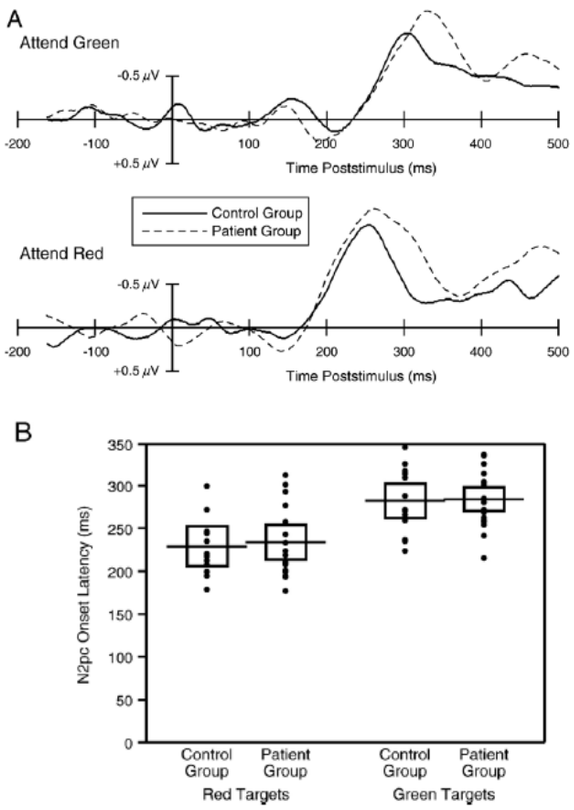

Fig. 8. (A) Grand average contralateral-minus-ipsilateral different waveforms from Luck et al. (2006)Experiment 1, averaged over the parietal, posterior occipital, lateral occipital, and posterior temporal electrode sites. Negative is plotted upward. (B) N2pc onset latency for each subject (filled circles), along with the mean and 95% confidence interval for each group. From Luck et al, 2006. Reprinted with permission.

A third experiment examined the categorization and response selection processes (Luck et al., 2009). This experiment used the P3 ERP and lateralized readiness potential (LRP) to identify when slowing occurred. The task was to respond with left or right hand depending on whether the stimulus was a letter or a digit. The response was reversed halfway through the session and the probabilities of letter or digit were adjusted throughout the sessions to produce a biased response for letters or digits or an equiprobable response. The P3 wave could be used to indicate the finish of perception and categorization and the LRP indicated the start of response preparation. Results showed no difference in latency of the P3 wave

(part A of Figure 9) but a significant difference between controls and schizophrenia groups in latency of the LRP (part B of Figure 9). This indicates that the stage that was taking the most time was the response selection stage.

Several fMRI studies of response selection have been reported on people with schizophrenia. The earliest study used a simple RT task with a flashing checkerboard with a motor response to look at hemodynamic response function in people with schizophrenia (Barch et al., 2003). It found patients to be slower in RT, but to activate the same general areas with the same general hemodynamic response function. They used the finding to support the idea that differences in fMRI activation in people with schizophrenia are reflective of a real difference in activation rather than some difference in coupling between neural activity and the hemodynamic response function.

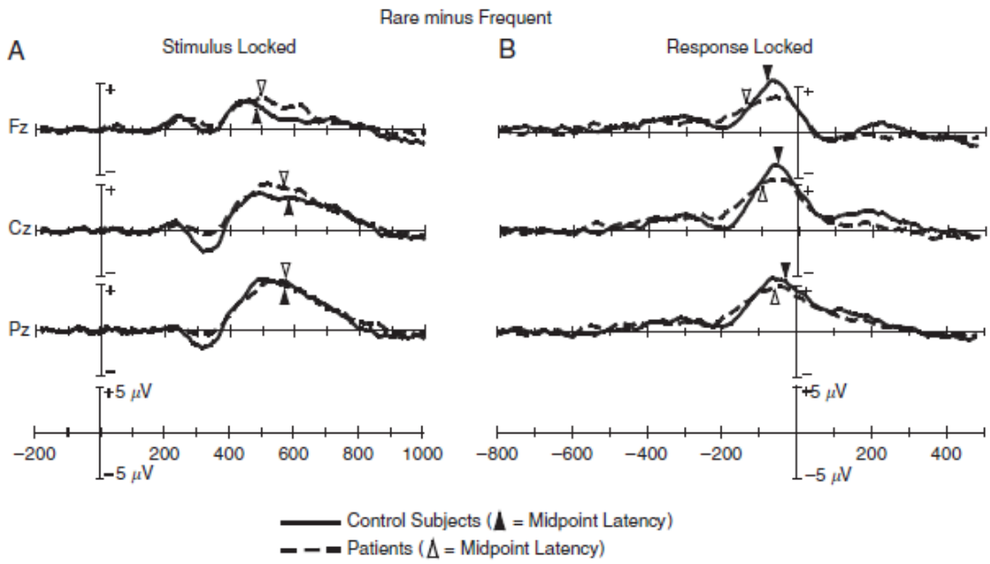

Fig. 9. Stimulus-locked (A) and response-locked (B) grand average ERP difference waveforms (rare minus frequent) from the patient and control groups at the frontal, central, and parietal midline electrode sites. Chart A shows the P3 wave and Chart B shows the LRP. Triangles indicate mean midpoint latency values. From Luck et al, 2009. Reprinted with permission.

Another study analyzed the data of a procedural learning study (Woodward et al., 2009). Although this study was set up to investigate procedural learning in schizophrenia, it included a block with random trials that could be analyzed versus fixation blocks. The task was a visual 4-choice spatially stimulus-response compatible task using 4 buttons on the dominant hand. The study included first-episode psychosis, chronic and first-degree unaffected sibling groups. The study found slower choice RT in all these groups compared to healthy controls, increased errors in patient groups, and increased BOLD activation in right dorsolateral prefrontal cortex (DLPFC, Brodmann Area 9) (see Figure 10). As well, a functional connectivity analysis using the right DLPFC area as a seed identified reduced connectivity in people with schizophrenia with many areas and found that connectivity between right DLPFC and right Brodmann area 40 correlated with RT in only patients, not controls. Overall, the results pointed towards choice RT fitting the criteria for an endophenotype.

Finally, another fMRI study used a difference between watching the visual stimuli and performing a motor response to remove visual activations and other common processes from the activation maps (McAllindon et al., 2009), and leave just the response selection and motor response processes. With a small sample size of 15 in chronic schizophrenia and healthy volunteer groups, the study found only a trend to lower activation in ACC in people with chronic schizophrenia, accompanied by an increase in RT.

In summary, response selection slowing has been investigated in people with schizophrenia with many different techniques and paradigms. A key future line of research is to understand when in the temporal sequence of cognitive processes the cognitive deficit appears in people with schizophrenia. Since spatial location of a deficit may in fact be in connectivity between functional areas in the brain, the temporal sequence may be the best clue to the deficit.

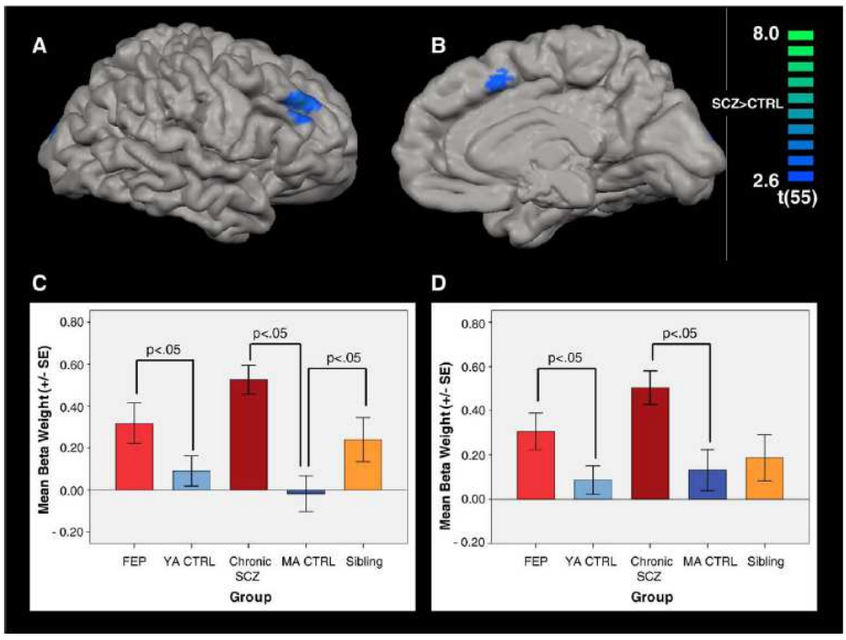

Fig. 10. Differences in brain activity between patients with schizophrenia, unaffected siblings, and healthy controls during choice reaction time task. Compared to controls, patients demonstrated greater activity during CRT blocks in right BA 9 (A) and right SMA (B). Activity in right BA 9 (C) and right SMA (D), in terms of task predictor beta weights. From Woodward et al, 2009. Reprinted with permission.

4. Models of response selection

Models of response selection have the potential to contribute greatly to the understanding of this process and how it can be affected by disease or neurological disorders. Specific theories can be developed and tested with reference to such models. Neuroimaging plays an important part in developing these models at the proper level to test theories of deficit.

There are many different types of models. A type that has been most researched is mathematical modelling. An early model of this type was Hicks' Law, which explained the dependence of reaction time on the number of choices:

$$\text{Mean RT} = K\log_2(n+1) \quad (1)$$

Where, K is a constant that changes for each individual, and
n is the number of choices

Various additions to the basic Hick's Law can account for the effect of frequency, the effect of sequence, the effect of discriminability and the effect of errors.

The most successful modern models are the Ornstein-Uhlenbeck diffusion model and the leaky competing accumulator model (Smith & Ratcliff, 2004.) Both models are for a 2-choice reaction time task and can predict most aspects of the RT distributions, including fast errors. In the leaky, competing accumulator model, 2 connected leaky accumulators gather evidence for their related response from the stimulus (see Figure 11). Accumulation is modelled as a stochastic process so that there can be variability in the RT results even when the stimulus is exactly the same, and so that mistakes can sometimes occur, as in behavioural results.

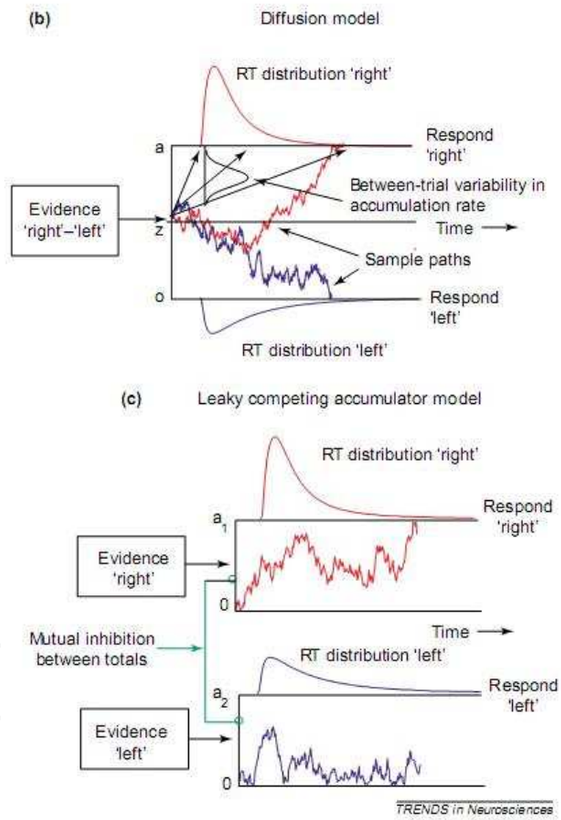

Fig. 11. Mathematical Models of Reaction Time (from Smith and Ratcliff, 2004) Reprinted with permission.

A simpler mathematical model is the linear ballistic accumulator model of Brown and Heathcote (Brown & Heathcote, 2008). This model uses linear rather than random walk accumulation with random starting levels in the accumulators. The model can successfully show the distribution of RT for multiple choice RTs, successfully repeat the pattern of correct and incorrect RTs, and has complete analytic solutions for multiple choice situations.

Another type of model is the computational model. These models are inspired by neural networks and take more or less biologically-principled views of the real neural networks that can be configured to response selection tasks, or whatever cognitive function is being modelled. These models can provide insight on the various levels at which they are modelled, and show the most promise in testing theories of deficit because of their biological relevance. Based on what has been discovered about the neurophysiology of the visual saccade task in monkeys, biologically-plausible neuronal simulations have been built that replicate real behavioural RT results (Wong & Wang, 2006; Lo & Wang, 2006). Wong's work modelled the basic task and they could use the model to show that the time integration in LIP neurons must be mediated by NMDA receptors rather than AMPA receptors. Lo and Wang's work was specifically trying to answer questions about the decision threshold in RT tasks and whether variability in the threshold could be modelled with a biophysically-based model. They found that a network including neocortex, basal ganglia and superior colliculus could perform the task, and that the basal ganglia was primarily responsible for the decision threshold. Although the work is specific to the visual saccade task, one can imagine a similar network being developed for a RT task involving manual response.

Lo and Wang's model is very suggestive for RT results in schizophrenia because of the connections of mid-brain dopamine neurons with neurons in the caudate (part of the basal ganglia). If a circuit involving the caudate is involved in setting decision threshold, it could be influenced by dopamine levels (Kiana, Shanks & Shadlen, 2006). We know that dopamine is implicated in schizophrenia, and the above model results suggest a mechanism how the abnormal dopamine levels could affect reaction times.

5. Conclusions

Recent neuroimaging research into the response selection deficit in schizophrenia as summarized in this chapter shows promise to unravel the details of why people with schizophrenia have slower and more variable reaction times. This progress appears at many different levels, from behavioural studies identifying performance differences in people with schizophrenia, to a more detailed understanding of the neural processes involved in response selection from basic animal and human research, to finding particular processes and areas showing deficit in people with schizophrenia, to testing of theories in computational models. The approaches that break the task into stages to investigate when the deficit occurs offer promise in finding the deficit, and the increasing sophistication of models offers promise in being able to test theories of deficits. A detailed understanding of a relatively simple cognitive task such as choice reaction time will improve understanding of neuroimaging results of other cognitive tasks.

The promise of this research and understanding of response selection slowing and cognitive deficits in general is, of course, recovery. Rehabilitation programs can be developed to target specific deficits, and research into neural plasticity shows promise that effective rehabilitation programs can offer real hope of recovery. In addition, new medicines could be developed to target underlying physiological deficiencies. But it will be a long hard road yet to reach this promise.

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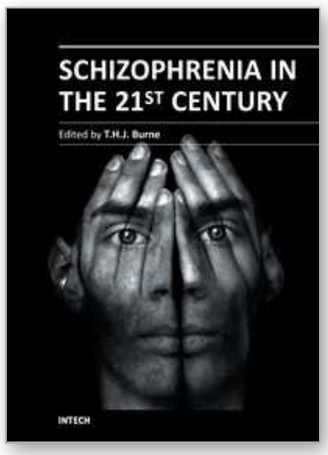

Schizophrenia in the 21st Century
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Schizophrenia is a poorly understood but very disabling group of brain disorders. While hallucinations and delusions (positive symptoms of schizophrenia) feature prominently in diagnostic criteria, impairments of memory and attentional processing (cognitive symptoms of schizophrenia) are attracting increasing interest in modern neuropsychiatry. Schizophrenia in the 21st Century brings together recent findings on this group of devastating disorders. We are still a long way from having effective treatment options, particularly for cognitive symptoms, and lack effective interventions and ways to prevent this disease. This volume covers various current options for therapy, clinical research into cognitive symptoms of schizophrenia and preclinical research in animal models.

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