Executive function in schizophrenia: what impact do antipsychotics have?

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Cognitive dysfunction is a major component of schizophrenia, with deficits in executive function particularly pertinent to successful daily living and outcome. Executive deficits and negative/disorganised symptoms remain relatively resistant to amelioration by antipsychotic medication in comparison to positive symptoms. While there is a relative paucity of data on the effects of antipsychotics on specific executive deficits, atypical antipsychotics would appear to be more beneficial than typical antipsychotics at improving these functions, with muscarinic, glutamatergic and cholinergic systems variously implicated. Recent research focusing on the relationships between specific symptoms and specific executive deficits holds important implications for future psychopharmacological interventions in the area by elucidating the neural substrates and pathways which underpin schizophrenic symptomatology. This review attempts to evaluate the research thus far for the specific executive components of spatial working memory (SWM), inhibition, sustained attention and set shifting. Issues significant to future psychopharmacology in the area are discussed, with particular emphasis on the need for a greater consensus in methodology and definition executive function research in schizophrenia. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS—schizophrenia; executive function; working memory; attention; set shifting; inhibition

INTRODUCTION

Schizophrenia affects approximately 1% of the population and shows comparative prevalence across culture and location (Thaker and Carpenter, 2001). It has diverse debilitating effects across interpersonal, occupational, social and academic domains (Wiersma et al., 2000), remaining one of the top causes of disability in the world (Murray and Lopez, 1997). The disorder is generally accepted to incorporate three main symptom factors, namely positive (hallucinations, delusions), negative (flattened affect, avolition, ahedonia, alogia) and disorganised (thought disorder, incoherence, inappropriate affect) (e.g. Andreasen et al., 1995; Moritz et al., 2001), although other studies have found both positive (e.g. Kay et al., 1987) and negative (e.g. Andreasen and Olsen, 1982) associations between the positive and negative symptom factors.

In addition to these symptom clusters, schizophrenia has been acknowledged to have cognitive deficits at its core since its conceptualisation as dementia praecox (Kraepelin, 1919), the latter emphasising a fragmentation of cognitive processes. There have been consistent findings of a widespread cognitive deficit in schizophrenic populations in the range of 1.0 to 1.75 standard deviations below the normal population mean (Gold, 2004). The areas primarily affected include those of executive function, attention, verbal memory, episodic memory and visuospatial and motor performance (Bilder et al., 2000). While verbal memory is acknowledged as one of the most important areas for functional outcome (e.g. Green, 1996), an in-depth examination of all affected cognitive components is beyond the scope of this review, which will concentrate on the executive functions of spatial...
working memory (SWM), sustained attention, set shifting and inhibition and their suitability as pharmacological targets in schizophrenia. The focus on the latter arises from the acknowledgement of executive function as fundamental to cognition in general and evidence suggesting its association with the presence of negative symptoms which are equally resistant to antipsychotic amelioration in many cases.

EXECUTIVE FUNCTION

The concept of executive function, in its simplest form, postulates a central system of higher-level cognitive abilities which enable an individual to plan and execute goal-directed operations (Velligan and Bow-Thomas, 1999). Incorporated within this concept are a number of cognitive skills such as planning, initiation and sequencing of behaviour, self-monitoring and inhibition of behaviour incompatible with a specific goal (Lezak, 1995).

Executive function is clearly impaired in schizophrenia with deficits evident in first episode non-medicated populations (e.g. Chan et al., 2006), relatives (e.g. Park et al., 1995) and those at high risk for developing schizophrenia (e.g. Smith et al., 2006). These deficits are also known to influence functional outcome (e.g. Green, 1996) and there are also some suggestions of the autonomous impact of negative symptoms on functional outcome, albeit this area remains unresolved (e.g. Velligan et al., 1997).

Recent work has focused on fractionating executive function into its component parts, such as sustained attention, set shifting, flexibility, working memory and response inhibition and examining each of these various subcomponents in relation to differential symptomatology (e.g. Brazo et al., 2002; Donohoe et al., 2006a). This fractionation approach has developed in response to inconsistent findings in the literature in an attempt to elucidate the underlying pathways responsible and may prove a useful approach in investigating the effects of various pharmacological agents on executive function in schizophrenia.

CURRENT PSYCHOPHARMACOLOGY IN SCHIZOPHRENIA

Atypical antipsychotics are currently the most utilised pharmacological agents throughout Europe and America for the treatment of schizophrenia. Despite their beneficial effects in alleviating positive symptoms the consensus is less clear with regard to their effects on negative symptoms and cognition. While Buckley (2001) emphasises the lack of clarity with regard to whether the effects of atypical antipsychotics on cognition are dependent or independent of reduction in positive symptoms, it is likely that antipsychotic medications work on different neural systems than those primarily involved in cognition and negative symptomatology (Green et al., 2004). It is generally accepted that atypical antipsychotics have greater benefits than typical antipsychotics in alleviating cognitive deficits (see Keefe et al., 1999 for review and meta-analysis). However, findings in the area may be confounded by the effects of high dosage in studies using typical antipsychotics, whereby the possibility of extra pyramidal side effects is increased (e.g. Mishara and Goldberg, 2004). More recently Keefe et al. (2004) have found little difference in effect between typicals and atypicals when compared at low doses of the former. Indeed, although effects are generally smaller, improvements in executive function have been found with typical antipsychotics (e.g. Mishara and Goldberg, 2004). Nonetheless, it is likely that atypical antipsychotics have greater beneficial effects (e.g. Bilder et al., 2002; Cuesta et al., 2001; Purdon et al., 2000), though not all agree (Goldberg et al., 1993; Green et al., 2002).

All atypical antipsychotics currently available act primarily on the dopamine system but also have a significant impact on other neurotransmitters such as serotonin. Keefe et al. (2006) suggest significant improvement across cognitive domains with olanzapine and risperdone, the latter showing beneficial effects on visuospatial memory. Olanzapine has been shown to show superior performance to both risperdone and haloperidol at improving executive function performance (Purdon et al., 2000) but Bilder et al. (2002) found olanzapine and risperdone to be superior to haloperidol but not different from each other or clozapine on global cognitive function. Lindenmayer et al. (1998) suggest clozapine has a comparable effect on executive function to risperdone.

Investigations of the cholinergic system, as outlined by Stip et al. (2005), have found that atypical antipsychotics increase acetylcholine release in the prefrontal cortex (PFC) and the hippocampus (Ichikawa et al., 2001) and indeed Tandon et al. (1991) suggest that decreased cholinergic activity might be associated with positive symptoms, thereby providing a possible explanation for the greater effects of atypical agents on positive symptoms. The latter author further suggests that muscarinic hyperactivity might be associated with the development of negative symptoms. There are also suggestions that nicotine administration ameliorates cognitive deficit in schizophrenia (e.g. Depatie et al., 2002), although Sacco
et al. (2006) found no effect of mecamylamine (a central nicotinic acetylcholine receptor antagonist) on cognitive function in schizophrenic non-smokers. In terms of anticholinergic agents’ effects on executive function, cholinesterase inhibitors have been shown to improve performance in areas such as planning and sustained attention (Stip et al., 2004), the latter an important fundamental area for the successful execution of all cognitive functions (Sarter et al., 2001).

The glutamatergic system has also come to the fore in the search for new antipsychotics, with N-methyl-d-aspartate (NMDA) receptor agonists shown to decrease negative symptoms and cognitive deficits (e.g. Stip et al., 2005). Furthermore, there is evidence of a direct influence of the noradrenergic system on prefrontal functionality, with projections from the locus ceruleus to the PFC influencing cognitions, in particular executive functions (Stip et al., 2005).

As such, evidence of psychopharmacological amelioration of cognitive deficits in schizophrenia thus far remains disparate and indeed two of the main issues impeding the development of new pharmacological agents aimed at improving executive function in schizophrenia are the determination of which approaches are most promising and also the lack of consensus in measurement and definition of cognitive processes generally (Green et al., 2004) and executive functions in particular. The subsequent review of the executive components of SWM, sustained attention, set shifting and inhibition (all of which show potential as discreet impairments) will attempt to elucidate these issues in relation to these executive functions.

SPATIAL WORKING MEMORY

Working memory is a dynamic system in which information is both stored and actively processed and the system is thought to be important for the generation of actions and intentions and for the unified operation of memory, language, comprehension and reasoning (Baddeley, 1996). Working memory deficits have been well documented in schizophrenia (e.g. Cameron et al., 2002; Pantelis et al., 2004) and are associated with poor social functioning (e.g. Park et al., 2006), thereby making these deficits important targets for interventions.

In the quest to find endophenotypes (trait markers) of schizophrenia, SWM has come to the fore as a probable candidate. First, many have found SWM deficits in unaffected relatives of those with schizophrenia (e.g. Cannon et al., 2000; Myles-Worsley and Park, 2002), unaffected co-twins (Johnson et al., 2003) and groups at high risk for psychosis (e.g. Smith et al., 2006). Furthermore, Cannon et al. (2000) found SWM impairment to be independent of general ability, attention and long-term memory, suggesting possible discreet impairment. There is much evidence to suggest an association between SWM and negative symptomatology (e.g. Cameron et al., 2002; Donohoe et al., 2006b; Pantelis et al., 2004), although there is also evidence to suggest an association with disorganisation symptoms only (e.g. Takahashi et al., 2005).

Pantelis et al. (2001, 2004) has suggested that this association rests on the involvement of the dorsolateral prefrontal cortex (DLPFC) in SWM and indeed some of the most consistent findings in the area of symptomatology have been with regard to negative symptoms and neuropsychological dependence on the DLPFC (e.g. Liddle, 1992; Pantelis et al., 2001). Goldman-Rakic et al. (2004) implicate prefrontal dopamine (D1) receptor activity or dysregulated signalling pathways in working memory deficits and highlight that hypodopaminergia in the PFC may underlie negative symptoms. Kindermann et al. (2004) found that in older schizophrenics there was normal or near normal activation of the DLPFC during SWM, but an aberrant pattern of brain response and indeed spatial functions have been found to be the least robust to illness duration in schizophrenia (e.g. Morrison et al., 2006). Kuperberg and Heckers (2000), however, point out that DLPFC function may depend on ‘task difficulty’, wherein function is only deficient when working memory load is high (e.g. Carter et al., 1998). Castner and Williams (2007) suggest the interaction of NMDA and D1 receptors in the PFC is important to prefrontal activity and hypothesise this interaction as a possible fundamental neural substrate for working memory.

Studies examining the effects of antipsychotics on SWM specifically are rare, but Meyer-Lindberg et al. (1997) suggest an enhancing effect from clozapine and zotepine, the latter to a greater degree. Manoach (2003) emphasises that the area has not been resolved and contradictory findings suggesting both hypofrontality and increased frontal activity make it difficult to extrapolate conclusions.

INHIBITION

Inhibition can be defined as the inability to deliberately inhibit a dominant, automatic or prepotent response when required (Rabbitt, 1997), while Fuster (1997) describes inhibitory control as playing a protective role in keeping behaviour, speech and thought from influences (external or internal) that may
interfere with them. Inhibitory impairments in schizophrenia have been found using the Stroop colour word test (Stroop, 1935) (e.g. Brazo et al., 2002; Donohoe et al., 2006a; Mahurin et al., 1998; Moritz et al., 2001); Tower of Hanoi type tasks (e.g. Chan et al., 2004; Gras-Vincendon et al., 1994); the Stop Signal task (Logan et al., 1984) (e.g. Badcock et al., 2002; Donohoe et al., 2006a) and antisaccade tasks (e.g. Curtis et al., 2001; Kumari et al., 2005).

When examined with regard to symptomatology, associations have been found both with negative symptoms only (e.g. Donohoe et al., 2006a; Mahurin et al., 1998) and disorganisation symptoms only (Brazo et al., 2002; Leeson et al., 2005). It is, however, prudent to consider various limitations when concluding from these studies. First, as a number of different instruments are utilised, the measurement of inhibition may be compromised by the involvement of other cognitive processes. Henik et al. (2002) have also shown that inhibition performance may be contextually dependent, with Henik and Salo (2004) suggesting performance depends on presentation, with delays increasing attentional demands and leading to difficulties.

Dollfus et al. (2002) suggest impaired inhibition as a possible endophenotype in schizophrenia. It has been found to be impaired in unaffected first-degree relatives (e.g. Curtis et al., 2001; Kumari et al., 2005), although other studies have found less clear evidence of impairment in relatives (e.g. Brownstein et al., 2003). While some postulate inhibition as a discreet, separable impairment in schizophrenia (e.g. Fuster, 1997), others suggest that it is actually subsumed by working memory (e.g. Goldman-Rakic, 1987) as they share common circuitry and inhibitory efficacy decreases as working memory load increases (Bunge et al., 2001). Barton et al. (2006), however, found evidence to support inhibition as a discreet component and indeed the fact that inhibition is not entirely affected by WM load suggests at least some discreet pathways. It is likely that instruments which tap more than one process impede the clarity of this issue.

Anterior cingulate cortex (ACC) activation has consistently been implicated in inhibition (e.g. Kerns et al., 2005; Nordahl et al., 2001), while Hester et al. (2004) found that ACC, PFC and parietal areas were the regions primarily activated in inhibitory tasks. These findings strengthen the hypothesis that output-monitoring ability may be involved in the process, especially in times of high conflict, as the ACC is known to be integral to conflict resolution and monitoring (e.g. Carter et al., 2001). There are some studies which suggest improvements in inhibitory control with atypical antipsychotics, including improved antisaccade performance with risperdone (Burke et al., 1998), and improvements in Stroop performance with olanzapine (Cuesta et al., 2001) and quetiapine (Velligan et al., 2002).

SUSTAINED ATTENTION

Attentional difficulties are among the most acknowledged in schizophrenia and there exists a multitude of evidence for such (e.g. Baerwald et al., 2005; Cornblatt et al., 1989; Heinrichs and Zakzanis, 1998). Generally, as Baerwald et al. (2005) highlight, impairment encompasses a decrement in performance over time and deficits in processing speed. In particular, sustained attention, as a subcomponent of executive function, has been well investigated.

One of the most utilised measures of sustained attention in schizophrenia is the Continuous Performance Task (CPT) (Cornblatt et al., 1988) and it has highlighted impairments in schizophrenics in many studies (e.g. Cornblatt et al., 1989; Kurtz et al., 2001). The relatively more recent Sustained Attention to Response Task (SART) (Robertson et al., 1997) has also been found to be sensitive to impairments in schizophrenia (e.g. Chan et al., 2004; Donohoe et al., 2006a). Exploration of the relationship between impairments in sustained attention and specific symptom clusters in schizophrenia have yielded conflicting results with the possible exception of the relatively consistent finding of no correlation with positive symptoms (e.g. Kurtz et al., 2001; Nieuwenstein et al., 2001). While Strauss et al. (1993) found a modest correlation between impairment and thought disorder measures, and Buchanan et al. (1997) found that a deficit group showed a greater level of impairment than a non-deficit group, the variation in symptom classification makes drawing conclusions difficult. Furthermore, while some have found an association between greater impairment and negative symptoms (e.g. Nieuwenstein et al., 2001), others have found no clear association (e.g. Donohoe et al., 2006a).

Numerous explanations for these inconsistencies have been postulated. Kurtz et al. (2001) implicate a diversity of symptom evaluation measures and sustained attention measures, the latter resting on the possibility that difficulties may reflect a working memory problem rather than a purely attentional one due to the high working memory load postulated to underpin sustained attention tasks. Indeed, Lee and Park (2006) point out that CPT has variously been
postulated to measure sustained attention, context processing and working memory.

Despite these conflicting findings, some have suggested sustained attention as a potential trait marker for the illness (e.g. Cornblatt and Malhotra, 2001) with evidence of deficits in unaffected first-degree relatives (e.g. Grove et al., 1991; Mirsky et al., 1995) and those with schizotypal personality disorders (e.g. Gooding et al., 2006). Deficits in this area also appear to be more prevalent among children of schizophrenics who go on to develop psychopathology (e.g. Erlenmeyer-Kimling and Cornblatt, 1987) and to be directly related to schizophrenia to a greater degree than other psychiatric illnesses (e.g. Nuechterlein, 1983). Nonetheless, other studies have failed to support these findings with both schizotypal participants (e.g. Lenzenweger, 2001) and those at high risk for developing schizophrenia (e.g. Cosway et al., 2002). The latter authors further found that sustained attention was spared in schizophrenic adolescents while most other areas associated with adult schizophrenic cognitive deficit were evident.

Sustained attention as an entity of its own is not well represented in the psychopharmacology literature and while McGurk et al. (2004) found improvement with olanzapine, others suggest it remains unaffected by medication (e.g. Michie et al., 2000). Thus, the evidence in this area of executive function remains inconsistent with regard to associations with symptom groups and psychopharmacology.

SET SHIFTING

Set shifting refers to the ability to shift ‘attentional set’ between multiple tasks, operations or ideas via the ability to disengage from an irrelevant stimulus and engage with a relevant one, thus responding adaptively in novel circumstances (Donohoe and Robertson, 2003). Shafritz et al. (2005) found that brain areas activated during set shifting tasks include the DLPFC, ACC and intraparietal sulcus.

The most common instrument purporting to measure this executive function is the Wisconsin Card Sorting Task (WCST) (Grant and Berg, 1948) and there is much evidence of general WCST impairment in schizophrenia (e.g. Daban et al., 2005; El Hamaoui et al., 2006; Heinrichs and Zakzanis, 1998). A number of possible explanations for these impairments in schizophrenia have been postulated, including response perseverations (Elliot et al., 1995) and failure to generalise learning (e.g. Pantelis et al., 1999). The latter author suggests that in comparison to patients with frontal lobe lesions, schizophrenics were more impaired on the concept formation required to learn set. Additionally, such impairment cannot be understood purely in terms of motivation or volition, with Hellman et al. (1998) finding that incentive has little effect.

There is some evidence suggesting set shifting impairment as an endophenotype in schizophrenia, with evidence of deficits in unaffected relatives (e.g. El Hamaoui et al., 2006) and of stability of deficits over time, irrespective of medication (e.g. Tyson et al., 2004). Alternately, Tunbridge et al. (2004) suggest inhibition of catechol-O-methyltransferase (COMT), important for the inactivation of dopamine, has been found to specifically improve extradimensional set shifting, while selective 5-HT6 antagonism has also been associated with improvements (e.g. Hatcher et al., 2005).

WCST is undoubtedly one of the most utilised measures in the pharmacological literature in schizophrenia, with numerous studies finding improvements in performance with clozapine (e.g. Lee et al., 1994), ziprasidone (e.g. Harvey et al., 2004), risperidone (e.g. Cuesta et al., 2001) and olanzapine (e.g. Harvey et al., 2003). The majority of studies in this area, however, propose WCST performance to be indicative of general executive function rather than specifying the component being measured.

Numerous studies have also examined WCST performance with regard to symptomatology and findings are far from conclusive. Associations with deficits have been found only for negative symptoms when compared to both positive (e.g. Cuesta and Peralta, 1995b; Mahurin et al., 1998; Chan and Chen, 2005) and disorganised symptoms (e.g. Mahurin et al., 1998). Moreover, Sanfilipo et al. (2002) found that as negative symptoms increased, cognitive flexibility decreased. Associations have been found between impairment and disorganised symptoms, but only when compared to negative symptoms (e.g. Moritz et al., 2001) while others have found associations with both negative and disorganised symptoms (e.g. Nieuwenstein et al., 2001). There are findings in relation to positive symptoms to suggest they are associated with better performance (e.g. Donohoe et al., 2006a) while some have found no association between performance and any symptom cluster (e.g. Daban et al., 2005; El Hamaoui et al., 2006).

Numerous explanations have been postulated for this inconsistency, many centring on the specificity of definition and measurement. To begin with, despite its widespread use, the construct validity of the WCST is not well established (Phillips, 1997; Rabbitt, 1997), with Miyake et al. (2000) highlighting how it has been
variously described as measuring ‘mental set shifting’, ‘flexibility’, ‘inhibition’, ‘problem solving’ and ‘categorisation’. There have also been suggestions of a relationship to working memory underlying the task (e.g. Stratta et al., 2001). Additionally, it has been shown to have poor test-retest reliability (e.g. Burgess, 1997; Phillips, 1997) and administrative and scoring difficulties (Axelrod et al., 1994).

DISCUSSION

There is little doubt that numerous avenues of research have opened up in the search for pharmacological interventions for executive deficits in schizophrenia, with both atypical antipsychotics and novel approaches showing promise. Although still an area fraught with inconsistency, there is clearly a commonality between executive deficits and negative/disorganised symptomatology, both on a behavioural level and with regard to their lesser response to anti-psychotic medications, thus meriting their investigation as targets for further psychopharmacological intervention.

A major issue pertaining to the progress of this research, however, is the lack of consensus in the literature on issues of both definition and measurement of executive components. Green et al. (2004) in outlining the MATRICS guidelines highlight this issue as pertinent to the ongoing development of pharmacological interventions in the area and there is little doubt that the lack of utilisation of a standardised format is preventing definite conclusions in many areas.

The wide use of the WCST (Grant and Berg, 1948) as a measure of general ‘executive function’ is problematic in an area such as schizophrenia, wherein impairments are discreet and diverse incorporating many brain regions and connections. The variability among people with regard to the extent, pattern and even presence of cognitive deficits makes drawing definite conclusions difficult. Indeed, there is a growing body of evidence to suggest that cognitive deficits are not global and generalised but rather specific, selective deficits highlighted by distinct patterns across various cognitive tasks (e.g. Baxter and Liddle, 1998).

While the WCST has proven a reliable measure of executive deficit in brain injured populations (e.g. Gansler et al., 1996), the lack of a similar focal deficit in schizophrenia means that one is unclear which aspect of executive function, if not all, are contributing to poor performance. Although Heinrichs’ (2004) meta-analysis found an effect size of 0.88 for WCST in schizophrenia, the latter comparable to that seen for frontal hypometabolism, it is unclear what is actually being measured or how many executive components are contributing. Functional imaging evidence also seems to support the idea that the WCST is not a specific enough measure, with Lie et al. (2006) finding that many areas associated with attention, working memory and set shifting were activated during the task and these activations varied depending on whether or not instruction was given. As such, it may be pertinent in light of the current focus on fractionation in the executive function literature, to adopt this approach in the determination of psychopharmacological effects particularly in light of the fact that executive components may index distinct behavioural outcomes and have been associated with functional outcome (e.g. Reeder et al., 2004).

There is no doubt that the fractionation approach is not without its difficulties (Burgess, 1997), and there are many intercorrelations evident between executive measures (Wilson et al., 1996), which Donohoe and Robertson (2003) suggest may be indicative of ‘cognitive congruence’, wherein executive functions are intertwined rather than mutually exclusive. Nonetheless, the adoption of this approach to executive function research in schizophrenia seems sensible in light of the suggestions that an intrinsic, unitary executive function does not exist in the disorder (Chan and Chen, 2005).

Given the importance of functional outcome as an index of pharmacological efficacy it is important to acknowledge suggestions that standard executive function tests may lack ecological validity (e.g. Cripe, 1996). Van Beilen et al. (2005) suggest standard test procedures strongly prompt certain behaviours, thereby negating the influence of voluntary effort and not reflecting real life function. As such, some standard tests which are administered in structured clinical settings may be underestimating the effect sizes of various executive component deficits on real life functioning. Semkovska et al. (2004), however, suggest that real life functional deficits are associated with negative symptom levels and poorer performance on clinical tests of executive function. Nonetheless, as Green et al. (2004) outline, the multitude of other supports necessary for successful functional outcome make parsing out the specific contribution of cognitive remediation complicated.

CONCLUSION

Executive function components are promising potential targets for pharmacological intervention in
schizophrenia, not least due to their probable associations with negative and disorganised symptomatology. Current antipsychotics show more efficacy in the amelioration of positive symptoms than both negative and disorganised symptoms, and the latter symptom clusters have shown associations with the executive components of SWM, inhibition, sustained attention and set shifting. These executive components are similarly resistant to current medications relative to positive symptomatology, implicating distinct neural networks and pathways. Although some atypical antipsychotics and novel interventions have been shown to remediate executive deficits, the variability in defining these functions and the assortment of measures purporting to reflect them make the determination of definite conclusions difficult. The fractionation of executive function may prove a promising approach in future psychopharmacology in the area but if solid conclusions are to be drawn from research in this area, it is imperative that a consensus on the definition and measurement of individual executive components is adopted.

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