

Journal of Psychopharmacology

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J Psychopharmacol 2011 25: 1207

DOI: 10.1177/0269881111414450

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Journal of Psychopharmacology
 25(9) 1207–1225
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 DOI: 10.1177/0269881111414450
 jop.sagepub.com



Evaluation of state and trait biomarkers in healthy volunteers for the development of novel drug treatments in schizophrenia

Ivan Koychev¹, Emma Barkus^{2,3}, Ulrich Ettinger⁴, Simon Killcross⁵, Jonathan P Roiser⁶, Lawrence Wilkinson⁷ and Bill Deakin¹

Abstract

Antipsychotic drugs are the mainstay of treatment for schizophrenia but they have little effect on core negative symptoms or cognitive impairment. To meet the deficiencies of current treatments, novel potential compounds are emerging from preclinical research but translation to clinical success has been poor. This article evaluates the possibility that cognitive and physiological abnormalities in schizophrenia can be used as central nervous system biomarkers to predict, in healthy volunteers, the likely efficacy of entirely new pharmacological approaches to treatment. Early detection of efficacy would focus resource on rapidly developing, effective drugs. We review the relevance of selected cognitive and physiological abnormalities as biomarkers in schizophrenia and three of its surrogate populations: (i) healthy volunteers with high trait schizotypy; (ii) unaffected relatives of patients; and (iii) healthy volunteers in a state of cortical glutamate disinhibition induced by low-dose ketamine. Several biomarkers are abnormal in these groups and in some instances there has been exploratory work to determine their sensitivity to drug action. They are generally insensitive to current antipsychotics and therefore their predictive validity cannot be established until novel, therapeutically useful drugs are discovered. Until then such biomarker studies can provide evidence of drugs engaging with the mechanism of interest and encouragement of the concept.

Keywords

Antisaccade, biomarkers, salience attribution, schizophrenia, schizotypy, signal detection task, smooth pursuit, synchrony, working memory

Background and rationale for using biomarkers in drug development for schizophrenia

The introduction of the first antipsychotic, chlorpromazine, in 1952 and the subsequent generation of typical and atypical D2 antagonists saw a dramatic improvement in the prognosis of schizophrenia and enabled the de-institutionalization of patients to care in the community. However, many patients continue to experience symptoms in addition to the burden imposed by central nervous system (CNS) and metabolic side effects. Most patients change their treatment within the first 18 months (Lieberman et al., 2005). Furthermore, the efficacy of current treatments is largely confined to reduced psychotic or positive symptoms, with limited efficacy on negative and deficit symptoms or on impaired cognitive function. Poor social and occupational functioning (Heinrichs, 2005) remains a common outcome. Finding new pharmacological approaches to tackle these deficits remains a major unmet need in the treatment of schizophrenia (Nuechterlein et al., 2008). In addition little progress has been made on a truly disease-modifying therapy that has the potential of preventing schizophrenia.

Scientific insights in cognitive neuroscience, neuropharmacology and genetics are producing an increasing number of

novel drug targets. This is matched by increasing numbers of candidate compounds through technological advances such as combinatorial chemistry and high-throughput screening (Hurko, 2009). Novel drug development has mostly focused on compounds affecting single neurotransmitter systems

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putatively implicated in the pathogenesis of schizophrenia (Roth et al., 2004). The main targets and compounds for improving cognition in schizophrenia involve glutamate (e.g. glycine, metabotropic, AMPA receptor modulators; glycine transporter antagonists), acetylcholine (muscarinic and α_7 -nicotinic receptor agonists), dopamine (e.g. D1 and D3 receptor agonists; D4 receptor antagonists; catechol-*O*-methyltransferase inhibitors) and serotonin (e.g. 5-[hydroxytryptamine]HT_{2A} and 5-HT₆ receptor antagonists; 5-HT_{1A} and 5-HT₄ receptor agonists) neurotransmitter systems (Gray and Roth, 2007). However, the increase in targets and new chemical entities has not so far translated into clinical efficacy. Most novel compounds fail at the initial tests of efficacy in human disease, phase 2 and 3 clinical trials (Hurko, 2010). A recent review showed that practically all the agents that are currently in phase 3 clinical trials have the same mechanism as the already available agents (D2 antagonism) (Gray and Roth, 2007).

Obstacles to novel drug development in schizophrenia

The high attrition rate for novel compounds has exposed several critical obstacles to drug development for psychiatric illnesses that may be particularly relevant to the development of an antipsychotic with potent cognitive enhancing action.

First, novel agents are classically screened on the basis of their molecular actions and efficacy in animal behavioural models. However, only 3–5% of the compounds that were effective in preclinical screens were launched on the market (Hurko, 2010). This suggests that while animal models may capture aspects of the main disease process, they are still far from being its reliable and precise replication (Marcotte et al., 2001).

Second, once a drug is introduced to a clinical population, its efficacy is assessed using traditional clinical end-points, such as clinical rating scales. Their sole dependence on the patients' reports and clinician's observations introduces a subjective element that reduces their sensitivity and precision (Jansson and Parnas, 2007). In addition, these end-points account poorly for the cross-ethnic differences in psychopathology (Brekke and Barrio, 1997), which makes international comparisons difficult. This has been further complicated by high placebo response rates, which are particularly problematic in clinical trials in psychiatry (Kemp et al., 2010; Kinon et al., 2011). All these factors obscure the true drug effects and inflate the sample sizes required to detect clinical efficacy in clinical trials.

The final and perhaps most important obstacle to novel drug development in schizophrenia is a conceptual one. In contrast to many physical diseases, the aetiology of schizophrenia remains unknown which makes the choice of appropriate targets for drug development especially risky. Several neurotransmitter systems have been implicated in the pathogenesis of psychosis but, as mentioned previously, few drugs targeting non-dopaminergic transmitters show evidence of efficacy (Miyamoto et al., 2005). Given the probable complex components in schizophrenia, attributing the disease to a disturbance in a single neurochemical system is likely to prove too simplistic (Roth et al., 2004).

Increasing the probability of technical success using biomarkers

The need to improve the probability of technical success of drug development has driven the identification and validation of biomarkers. A biomarker is defined by the United States Food and Drugs Administration (FDA) as 'A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention' (www.fda.gov). Biomarkers have the potential of augmenting the chances of successful drug development through better target validation, provision of surrogate end-points and patient segmentation (Breier, 2005).

Target validation. Biomarkers relevant to target validation probe either disease-specific or drug activity processes. Disease biomarkers are used to explore the biological mechanisms involved in the pathophysiology of disease. This information can then be used to improve the diagnosis of the condition, to mark its progression and to develop pathophysiologically relevant animal models. For instance, the finding of decreased TD4 cells in HIV gave not only an insight into the pathophysiology of the condition, but also provided a practical measure to track its outcome. Drug activity biomarkers provide information on whether the drug interacts effectively with its target in humans (Breier, 2005).

Clinical surrogates. Biomarkers that consistently predict traditional clinical end-points could replace them and become 'clinical surrogates'. Clinical surrogates, being inherently more precise, reliable and replicable than traditional end-points, could allow the detection of efficacy in smaller clinical trials. Also, classical clinical end-points, such as survival and quality of life, inevitably require long-term follow-up. If a clinical surrogate predicts long-term treatment outcomes, however, it could reduce the duration of studies testing long-term benefit. Examples of successful clinical surrogates include blood cholesterol (predictor of cardiovascular mortality) and solid tumour size (predictor of mortality from a neoplastic cause). The MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) initiative has been developing a cognitive battery with the goal of providing of clinical surrogates for trials of cognitive enhancing drugs (Buchanan et al., 2007).

Patient segmentation. Some biomarkers also have the potential to stratify patients according to their likely treatment response or sensitivity to side effects. Utilizing such biomarkers could help reduce the sample sizes of clinical trials by allowing selection of more homogeneous patient populations in phase 2 and 3 clinical trials, which in turn reduces the variability of treatment response and decreases the likelihood of study discontinuation due to side effects.

Uncovering the likely drug failures using biomarkers

Biomarkers could improve the chances of technical success of a drug by refining its targets, allowing its specific and precise

assessment and selecting patient groups that are most likely to benefit. However, in the current situation of unclear pathophysiology of the main disease process, the vast majority of novel schizophrenia compounds are destined to fail. Therefore, a mechanism is needed to determine the likely failures as early as possible in their development and redirect resources to more promising compounds. This ‘quick win, quick kill’ approach aims to identify the likely failures as early as the phase I registration trial (Breier, 2005). Central to this idea are proof of concept studies which function by selecting only a subgroup of patients that is more likely to respond or by recruiting groups of individuals that have only limited symptom profile, that is, surrogate populations (Hurko, 2009). Proof of concept studies precede the costly phase 2 clinical trials which use more rigid diagnostic criteria, heterogeneous populations and traditional clinical endpoints.

Biomarkers are a key component of this strategy, as they can provide the precise assessment of efficacy that these clinical trials of small sample size and short duration require. The biomarkers for phase I ‘proof of concept’ studies are used to guide internal decision-making and early resource allocation and therefore do not need to undergo the same level of validation as clinical surrogates. Instead, their usefulness is determined by their sensitivity to the disease process (both in patients and in surrogate populations) and to the action of drugs that a prospective compound is aiming to emulate.

Biomarkers in surrogate populations

Surrogate populations are defined as groups that feature a component of the main disease process but do not have the fully developed condition. Many medical disorders can be seen extremes of normally distributed functions such as blood-pressure in hypertension and glucose regulation in diabetes. In psychiatry, anxiety and depressive neuroses have long been viewed as extremes of normal variation in fearfulness and mood. The idea that psychoses may represent extremes of normally distributed cognitive functions – such as reward processing (aberrant salience hypothesis), perception (hallucinations extended from vivid mental imagery) and frontal lobe executive function – is gaining momentum. The continuum view of physical and psychiatric disorders is encouraged by the absence of major gene effects, suggesting that many genes of small effect contribute to risk. This increases the likelihood that many individuals in the general population will have some of these genes and therefore may express some of the phenotype associated with the full disease.

The appeal of proof-of-concept biomarker studies in surrogate populations lies in their practicality, as they involve populations that are easier to recruit than homogeneous patient groups and lack the major confounding factors of patient samples. In respect to cognition in schizophrenia, such potentially confounding factors are prior or concomitant drug treatment, chronicity, lack of cooperation, lower educational and premorbid intelligence quotient (IQ) levels. At the same time biomarkers in these samples may be more sensitive to drug effects than unselected healthy volunteers because

they share elements of the disorder. In addition, these samples provide the option of testing potentially disease-modifying therapies, as they feature the vulnerability pattern, but not the fully developed disease.

The authors have been interested in the strategy to improve the sensitivity of biomarkers for drug action by evaluating them in three surrogate groups with increased psychosis liability: (i) unaffected relatives because they share genetic vulnerability, (ii) people with schizotypal personality because of their predisposition to symptoms, and (iii) volunteers with experimental drug-induced schizophrenia-like states.

Biomarkers in relatives: endophenotypes and vulnerability

One healthy group who might show greater sensitivity to novel schizophrenia treatments are the unaffected first-degree relatives of patients with schizophrenia, since they will carry more susceptibility genes than found in the general population, but in insufficient number or combination to develop psychosis or to overcome unknown protective factors. Several neurocognitive characteristics that are shared between relatives and patients have been reported (Allen et al., 2009) and some are described in later sections. These changes imply the presence of shared susceptibility genes and lie closer to genetic mechanisms of disease than the overt clinical phenotype. Therefore, these biomarkers are a subgroup of the disease-specific biomarkers that relate to genetic vulnerability only. With the inclusion of a number of other criteria they have been termed endophenotypes (Gottesman and Gould, 2003).

In the psychosis literature they have principally concerned cognition or information-processing. Successful identification of endophenotypes could reveal neural pathways that underlie the schizophrenia phenotype. However, selecting volunteers for drug-efficacy biomarker studies on the basis of familial liability will require both openness and tact to avoid understandable fears of being treated like their ill relatives and identified with disorder. Drugs that prove effective on biomarkers in relatives would have the potential to affect mechanisms of vulnerability and therefore prevent onset of disorder in those with at-risk mental states. There is some tentative evidence that relatives of patients with schizophrenia who express psychosis liability characteristics, benefit functionally from treatment with a low-dose atypical antipsychotic (e.g. Tsuang et al., 1999).

Biomarkers in schizotypy: correlates of psychopathology

In keeping with the continuum view of schizophrenia, systematic surveys suggest that brief schizophrenia-like experiences and beliefs are surprisingly common in the general population and are also more prevalent among first-degree relatives of patients (Van Os et al., 1997). Such phenomena may be sufficiently intense and long-standing to interfere with everyday functioning and so warrant the diagnosis of schizotypal

personality disorder. However, much evidence suggests that schizotypal personality traits are continuously distributed in the general population and that schizotypal traits may be quite prevalent in people with normal social and occupational functioning. In a later section we discuss evidence that healthy volunteers with high scores on schizotypal personality questionnaires show patterns of neurocognitive performance similar to these seen in schizophrenia. Selecting schizotypal populations may enhance the sensitivity of drug efficacy biomarker studies in the healthy population. Indeed, schizotypal symptoms themselves may be sensitive to new antipsychotic drugs and benefit from such interventions.

Biomarkers in drug-induced states

Dopamine. Administration of dopamine-releasing agents such as amphetamine and methylphenidate has been used extensively to model the symptoms of schizophrenia. These agents induce an acute schizophrenia-like syndrome in heavy users (Connell, 1958), exacerbate positive symptoms in patients (although improvements in spontaneity and activation have also been reported), and induce symptoms when given experimentally to volunteers. However, high doses are required to induce paranoid ideation and hallucinations and acute doses do not reproduce the cognitive and negative symptoms of schizophrenia. These findings, along with the demonstration that antipsychotic drugs block the behavioural effects of amphetamine gave rise to the theory that antipsychotics work through dopamine antagonism and the corollary hypothesis that schizophrenia is due to excessive dopaminergic neurotransmission. That enhanced dopamine release occurs in schizophrenia has now been firmly established by positron emission tomography (PET) measuring dopamine displacement of D2 radioligand binding (Abi-Dargham et al., 2000; Laruelle et al., 1996). Reports of increased uptake of fluoroDOPA suggest presynaptic dopamine neurones are more active in both acute and prodromal patients (Howes et al., 2009; McGowan et al., 2004). However, only subcortical striatal dopamine function has been quantifiable with these techniques and indirect evidence suggests that frontal cortical dopamine release may be reduced in schizophrenia. Indeed an important theory suggests that the primary abnormality in schizophrenia may be decreased frontal dopamine function with secondary increases in subcortical dopamine (Davis et al., 1991; Weinberger et al., 1988), the former mediating impaired cognition and negative symptoms, and the latter, positive symptoms.

How increased striatal dopamine release translates into positive symptoms is not clear. Dopamine clearly has an important role in reward in which its release by unexpected rewards (reward prediction error) triggers new learning. This has been visualized in humans, for example, in a study in which reward prediction error was associated with activity in dopamine areas that was attenuated by the dopamine antagonist haloperidol and facilitated by the dopamine precursor L-DOPA (Pessiglione et al., 2006). Excessive dopamine release in schizophrenia is postulated to result in aberrant reward learning and the formation of positive

symptoms (Kapur, 2003). Biomarkers based on reward prediction error are discussed in a later section.

Dopamine modulates frontal executive function and working memory (Goldman-Rakic, 1994). However, the relationship may not be linear. Literature on studies with animals and humans suggests that enhancing dopamine function from a low baseline improves executive functions, whereas increases beyond an optimal level result in decreases in executive function, therefore suggesting an inverted U-shape relationship. A further complication is that D1 and D2 receptors may exert opposite influences on frontal executive function. The empirical evidence suggests acute amphetamine challenge improves rather than disrupts cognition in patients with schizophrenia (Pietrzak et al., 2010). The improvement may be explained by a reversal of deficient stimulation of D1 receptors in schizophrenia that predominate in frontal cortex. As a result of this development, the experimental application of acute amphetamine challenge has recently shifted towards improving performance in states of suboptimal cognition and this is reviewed in later sections.

It should also be noted that differences exist between the effects of acutely and chronically administered amphetamine. Repeated administration of amphetamine in experimental animals can result in increased hyperactivity responses and other effects of amphetamine. This is known as amphetamine sensitization and has been proposed as a model for schizophrenia. Furthermore, sensitized animals also show evidence of cognitive deficits. Limited evidence suggests that amphetamine sensitization can be demonstrated in healthy volunteers and further exploration of cognitive biomarkers in this paradigm would seem worthwhile. It might be possible, for example, to find drugs that prevent sensitization without blocking the effect of amphetamine, and these might be useful preventative treatments in high-risk groups (Featherstone et al., 2007).

Corollary hypothesis acetylcholine. Administration of the dissociative anaesthetic agent ketamine in sub-anaesthetic doses to healthy volunteers induces suspiciousness, thought disorder, some of the negative symptoms of schizophrenia and impairs performance on working memory (Deakin et al., 2008; Krystal et al., 1999; Pomarol-Clotet et al., 2006). Ketamine blocks the ion channel associated with the *N*-methyl D-aspartate (NMDA) glutamate receptor. The psychotomimetic effects of NMDA channel blockers gave rise to the glutamate deficiency theory of schizophrenia. However, this is now better termed the NMDA deficiency hypothesis because drugs such as ketamine produce a paradoxical disinhibition of cortical glutamate release that acts on non-NMDA receptors. Many of the subjective and behavioural effects of ketamine can be blocked by agents that decrease glutamate release (Deakin et al., 2008). Thus increased glutamate release may be responsible for psychosis-like symptoms after ketamine, as has been suggested for the symptoms of schizophrenia (Deakin and Simpson, 1997). Whether there is a primary loss of NMDA receptors in schizophrenia is not clear, although this has been described in post-mortem hippocampus and in an in-vivo radioligand-binding study using

single positron emission tomography (Law and Deakin, 2001; Pilowsky et al., 2006).

The NMDA deficiency theory of schizophrenia has recently become pleasingly unified with gamma-aminobutyric acid (GABA) deficiency theories by evidence that a subclass of GABA interneurons that synchronizes the firing of pyramidal neurones is driven primarily by NMDA receptors (Belforte et al., 2010). These so-called fast-spiking interneurons are thought to correspond to these containing parvalbumin, which have repeatedly been reported to be deficient in post-mortem brain in schizophrenia (Lewis and Moghaddam, 2006). Thus ketamine and related drugs may mimic NMDA hypofunction, impaired GABA neurotransmission and disinhibited glutamate release which is hypothesized to occur in schizophrenia. In-vivo methods of quantifying GABA and glutamate function are needed to test these theories.

The cholinergic system has also been implicated in drug-induced psychotics. The administration of anticholinergic agents, such as scopolamine or atropine, is known to have the potential of causing 'antimuscarinic psychosis', a state that shares some of the behavioural features of endogenous schizophrenia (Minzenberg et al., 2004; Perry and Perry, 1995; Perry et al., 1978). Procyclidine, another antimuscarinic agent, was shown to retard the antipsychotic effects of flupentixol in patients (Johnstone et al., 1983). Together with data showing alterations of the muscarinic and nicotinic receptors in schizophrenia (Terry, 2008), this evidence has suggested that the acetylcholine system may be important in the pathogenesis of schizophrenia. Cognition is a likely target of a cholinergic disturbance (Minzenberg et al., 2004), as this neurotransmitter system is known to play an important modulatory role in memory, learning and synaptic plasticity (Sarter and Bruno, 1997). In demonstration of this, the use of cholinesterase inhibitors such as donepezil in Alzheimer's disease has been linked to slowing of the progression of cognitive deficits in this condition (Birks, 2006). Unlike ketamine, however, procyclidine and other antimuscarinic agents are limited in their use as pharmacological models of schizophrenia owing to their unfavourable side effects profile.

Purpose of the review

The second part of this article reviews the validity of several neurocognitive biomarkers from the major areas of interest in the literature with some more novel potential biomarkers developed by the authors. The emphasis is on potential biomarkers of drug efficacy in healthy volunteers that could be used in large-scale multicentre studies. We focus on neurocognition because it is free of preconceptions about the neurochemical actions necessary for efficacy of a new drug and the need for treatments that improve cognition and negative symptoms. Functional brain imaging using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) is informative at identifying the involvement of neural systems in cognitive functioning. Neuroimaging is therefore showing promise as a modality for detecting drug-efficacy but there are many technical issues and it is beyond

the scope of this article to provide a meaningful review of imaging biomarkers.

The review assesses selected neurocognitive biomarkers according to their:

- reliability (consistent effects reported by different laboratories or over time);
- criterion validity (abnormal in criterion groups: patients, unaffected relatives, high schizotypes and after amphetamine or ketamine in healthy volunteers);
- predictive validity (sensitive to the action of compounds effective in schizophrenia or cognition); and
- construct validity (relates to a known neurobiological system implicated in the disorder).

The importance of establishing the reliability and sensitivity of cognitive tests as end-points for clinical trials in schizophrenia has been recognized by the MATRICS initiative (Harvey et al., 2010). However, these studies focus solely on samples of patients with schizophrenia and the results are useful in terms of selecting and standardizing reliable cognitive tasks as clinical end-points. However, as discussed previously, the various confounds in this group (chronic disease and treatment, polypharmacy, institutionalization, florid positive symptoms, reduced cooperation) limit the conclusions that can be drawn regarding the pathophysiology of the subtle cognitive deficits and the disease. In an attempt to address these limitations, MATRICS recommends that participants have not more than moderate scores on formal thought disorder, hallucinations and delusions, negative and depressive symptoms, have minimal extrapyramidal symptoms, have been maintained on the same dose for 2–4 weeks and take only one antipsychotic (<http://www.matrics.ucla.edu/matrics-recommendations-frame.htm>). This limits the number of appropriate participants and still does not fully account for all confounds. In this review, the focus is on healthy volunteer criterion groups that provide a different viewpoint of the pathophysiology (genetic, psychopathological and molecular) with little or no impact of these confounding factors. This approach may contribute to our understanding of the mechanisms behind cognitive abnormalities in schizophrenia and accelerate the early evaluation of novel drug treatments.

Another relevant project is the CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) initiative (Carter and Barch, 2007) which aims to identify promising measures of perception and integration for validation as biomarkers for pathogenesis and drug development. One mature measure that already meets many CNTRICS criteria is pre-pulse inhibition of the startle response (Green et al., 2009). The literature, including many studies in healthy criterion groups has been extensively reviewed and is therefore not considered further here (Swerdlow et al., 2008).

We begin with working memory, one of the MATRICS domains, since a number of studies have explored abnormalities and drug effects in healthy criterion groups. We include some less well-validated tasks involving learning and perception that have an interesting theoretical background. From the extensive literature on eye-movement control and EEG biomarkers in schizophrenia, we have focused on newer measures and findings.

Validity of cognitive and physiological biomarkers of cognitive processes related to schizophrenia

Working memory: N-back and spatial working memory

Working memory (WM) refers to a process for holding and managing information 'online' over short periods of time, allowing its manipulation and usage in reasoning, comprehension and decision-making. The distinction between short-term memory and working memory is subtle and not always consistent (Reichenberg and Harvey, 2007). Working memory generally implies that the information is both stored and manipulated. It has been proposed that separate systems for the maintenance of verbal and visuo-spatial information exist (Baddeley, 1986). In accordance, the working memory tasks used in schizophrenia research as a rule involve either of the two modalities (Lee and Park, 2005).

Paradigm description. In the N-back task, a series of digits is presented and participants are required to respond if the current digit is the same as one presented N trials previously, where N varies between 0 and 3 in different trial blocks. This requires that the current rule is held in mind and that the relevant digit is updated from trial to trial. However, the task also draws on other cognitive processes such as response inhibition, strategy formation and checking. Spatial working memory involves remembering locations of objects. Computerized tasks such as the Cambridge Automated Test Battery (CANTAB) (Cohen and Servan-Schreiber, 1992) often require a visual search of locations to collect a target object. These, now empty, locations need to be avoided to efficiently collect remaining targets. Thus a constant updating of memory of searched locations is required. Again processes such as strategy formation and behavioural inhibition are required.

Construct validity. Classic, single cell recoding experiments in primates by Goldman-Rakic showed that cells in the dorso-lateral prefrontal cortex represent the spatial location of a cue over short delays until the information is used to obtain a reward (Goldman-Rakic, 1994). Functional imaging studies in humans confirm that working memory paradigms engage a dorsal network including dorsolateral prefrontal cortex and that these responses are abnormal in schizophrenia (Callicott et al., 2003).

Criterion validity

Patients, relatives and high schizotypes. Meta-analyses have indicated that patients with schizophrenia are significantly impaired on both verbal and visuo-spatial WM tasks (Lee and Park, 2005). WM deficits are stable across time and fluctuations in clinical status (Hill et al., 2004) and are present before the initiation of treatment (Barch et al., 2001). First-degree relatives also appear to be affected, with effect sizes ranging from small to moderate (Snitz et al., 2006). WM deficits have also been reported in schizotypal individuals with (Johnson et al., 2003) and without (Park and McTigue, 1997) family history of schizophrenia. Although WM is strongly

correlated with IQ, deficits that survive correction for reduced IQ have been reported in patients and high-risk subjects (O'Connor et al., 2009; Zanelli et al., 2010).

Glutamate antagonist challenges. Most studies in healthy volunteers have shown that ketamine impairs WM performance, the effects being stronger when the task requires manipulation of information; affinities with the WM deficits of schizophrenia have been noted (Fletcher and Honey, 2006, Morgan and Curran, 2006).

Predictive validity

Dopamine antagonists. Studies in patients treated both acutely and chronically with typical antipsychotics have found no beneficial effect on cognitive function (Meltzer and McGurk, 1999), although positive findings have also been reported (Keefe et al., 2007). The benefit of atypical antipsychotic therapy on WM is most likely to be marginal (Heinrichs, 2005) despite some studies reporting modest improvement (Houthoofd et al., 2008; Meltzer and McGurk, 1999; Purdon, 1999).

Dopamine agonists. In healthy volunteers, compounds that increase dopamine activity have generally been shown to improve WM. Amphetamine has been demonstrated to improve WM, especially in those individuals with low baseline performance (Mattay et al., 1996, 2000). Similar effects are reported with methylphenidate (Elliott et al., 1997, Mehta et al., 2000; but see Turner et al., 2003). The selective D2 agonist, bromocriptine, also improved performance on spatial WM tasks (Kimberg et al., 1997; Luciana et al., 1998; but see Kimberg et al., 2001). The mixed results of D2 agonism could be interpreted in the framework that sees D1 receptor agonism as the key factor in cognition enhancement. In demonstration of this, the disruption of WM induced in healthy volunteers by a D2 antagonist challenge was alleviated by pergolide, a mixed D1/D2 agonist, but not the D2 agonist bromocriptine (Muller et al., 1998).

There are almost no studies testing the prediction that dopamine agonists, by reversing the putative deficits in frontal dopamine function, would improve WM in schizophrenia. The obvious risk would be that psychotic symptoms would be exacerbated. One study reported that a single dose of amphetamine enhanced WM performance in schizophrenic patients taking antipsychotics (Barch and Carter, 2005). However, data have emerged on the efficacy of dopamine agonists in improving WM in schizotypal personality disorder (SPD). First, acute amphetamine benefited WM in SPD but not in other personality disorders (Kirrane et al., 2000). Again, the poorer baseline performers improved the most. Enhancement of cognition in SPD by dopamine agonism may also hold true for chronic treatment, as pergolide improved WM after 4 weeks' treatment in SPD (McClure et al., 2010).

Other agents. Cholinergic drugs modulate WM performance. Both muscarinic and nicotinic receptor antagonists

impair WM performance in healthy volunteers (Green et al., 2005; Thompson et al., 2000). In one study abstinence from smoking in patients was associated with impaired WM performance but not in non-schizophrenic smokers and this was reversed with smoking reinstatement (Sacco et al., 2005). Freedman et al. (2008) reported beneficial effects of a novel nicotinic agonist on some measures of WM in non-smoking patients along with improved negative symptoms. Cholinesterase inhibitors, on the other hand, improve WM in healthy volunteers (Furey et al., 2000a, 2000b). Studies exploring the potential of compounds stimulating the cholinergic system as an adjuvant therapy in patients largely report improved executive function (Ribeiz et al., 2010).

There is much interest in the role of impaired GABA function, possibly driven by deficient NMDA glutamate neurotransmission (see below), in the impairment of WM in schizophrenia. Lewis et al (2008) reported that the alpha-2 GABA-A agonist MK-0777 improved performance in a N-back task in 9 patients with chronic schizophrenia compared to controls. This was accompanied by changes in EEG and a continuous performance task (see below). This study has encouraged a larger clinical study that found no benefit on cognitive impairment in schizophrenia (Buchanan et al., 2011). However, sedative effects may have obscured clinical benefit and further studies with more potent agonists remain warranted.

Reward learning: the salience attribution test

Schulz et al. (1997) demonstrated that the presentation of unexpected (i.e. unpredicted) food rewards activates dopamine neurones in experimental animals. This is thought to act as a 'prediction error' or teaching signal. Any initially neutral cue (stimulus) that predictably precedes a reward will itself acquire the ability to activate dopamine neurones. In this way predictive cues become imbued with 'motivational salience' (Berridge and Robinson, 1998) and are able to capture attention and guide goal-direct behaviour. It has been hypothesized that in psychosis dysregulated dopamine release provides an inappropriate prediction error signal during the processing of irrelevant stimuli. This is thought to result in the inappropriate assignment of salience to external stimuli and internal representations such as thoughts or memories (Kapur, 2003). According to the aberrant salience hypothesis, delusions and hallucinations form as cognitive misattributions of the origin and significance of the unusual and repeated experience of many inappropriately salient stimuli.

Task description. Studies exploring salience attribution use cognitive psychology paradigms in which stimuli are either coupled with reward or not. The degree of correct and aberrant learning is inferred from behavioural measures, including choices, reaction times or participant awareness judgements (Roiser et al., 2009). For example in the Salience Attribution Test (SAT), coloured images of household objects or animals are presented prior to responding for possible rewards (money). One stimulus dimension (e.g. red vs. blue – relevant dimension) very reliably predicts the availability or non-availability of money, while the other (e.g. animals vs. household

objects – irrelevant dimension) has no bearing on the outcome. The rewarded stimulus feature (e.g. blue) promotes faster responding for reward relative to the unrewarded one (e.g. red), providing a measure of implicit adaptive (i.e. appropriate) salience; participants are also able to report this association overtly using visual analogue scales (explicit adaptive salience). Faster responding/greater reward rating occurring to one of the irrelevant features over the other (e.g. animals faster over household objects) indicates aberrant salience.

Such a distinction between adaptive and aberrant salience is important to directly test the aberrant salience hypothesis, since demonstrating an absence of normal reward processing is not necessarily directly indicative of the presence of context-inappropriate associations, the central tenet of this model. The first study to investigate behaviour on the SAT in patients with schizophrenia reported elevated explicit aberrant salience in patients with delusions, but not in those without (Roiser et al., 2009), consistent with the aberrant salience hypothesis (Kapur, 2003).

Construct validity. In apparent variance with the salience attribution hypothesis, functional imaging studies report reduced ventral striatal hemodynamic responses during reward cue conditions (Juckel et al., 2006b; Schlagenhauf et al., 2008) in patients with schizophrenia; this effect also correlated with negative symptoms. The proposed explanation for this paradoxical finding is as follows: in the context of many stimuli of heightened significance generally, reward-related cues may not differentially activate the ventral striatum, and thus fail to motivate behaviour (Roiser et al., 2009; Ziauddeen and Murray, 2010). Furthermore, explicit aberrant salience in the SAT was associated not only with delusions but also with negative symptoms (Roiser et al., 2009). Interestingly, in healthy volunteers, the degree of aberrant explicit salience correlated with haemodynamic responses in the prefrontal cortex, hypothesized to contribute to negative symptoms (Juckel et al., 2006b). Such findings highlight the importance of the distinction between negative symptoms, including anhedonia, that are secondary to the psychotic state, and enduring negative symptoms in the absence of psychosis (primary negative symptoms) that have a separate pathogenesis that is not responsive to antipsychotic drugs. The construct validity of the aberrant salience measurements provided by the SAT has also been investigated using principal components analysis in healthy volunteers (Schmidt and Roiser, 2009). This study found that aberrant salience was not related to potentially confounding measures including WM, selective attention, latent inhibition or reward learning.

Criterion validity

Patients, relatives and high schizotypes. Studies using reward-based paradigms have reported consistent abnormalities in patients with schizophrenia (Murray et al., 2008a, 2008b; Waltz and Gold, 2007), especially in those with delusions (Roiser et al., 2009), as mentioned previously. Also, aberrant salience has recently been linked to high levels of schizotypy (Housden et al., 2010; Roiser et al., 2009;

Schmidt and Roiser, 2009). There are currently no data regarding unaffected relatives of patients with schizophrenia, but evidence from psychophysical experiments suggests that abnormalities in reward processing increase linearly with genetic risk (Glatt et al., 2006).

Predictive validity

Dopamine antagonists. Normalization of aberrant salience with successful antipsychotic treatment has been reported in patients using the SAT (Roiser et al., 2009). As predicted by the aberrant salience hypothesis, patients taking antipsychotics also scored lower on adaptive salience than controls (Kapur, 2003). In addition, the antipsychotic drugs haloperidol (Pessiglione et al., 2006) and olanzapine (Abler et al., 2007) have been reported to attenuate reward-related responses in the ventral striatum of healthy volunteers. However, Juckel and colleagues reported a relative sparing of striatal reward-related responses in patients administered atypical but not typical antipsychotic drugs (Juckel et al., 2006a). More drug studies using the SAT in healthy volunteers and criterion groups are required before the predictive validity of the task can be evaluated.

Dopamine agonists. The role of dopamine in aberrant salience attribution is supported by a study utilizing amphetamine challenge in healthy volunteers, which reported a loss of specificity of haemodynamic responses in the ventral striatum to rewards relative to punishments (Knutson et al., 2004). The effect of dopamine agonists on SAT performance has not yet been investigated.

Biconditional learning

Cohen and Servan-Schreiber (1992) have attempted to account for a broad range of cognitive deficits observed in schizophrenia by appealing to a unitary mechanism. They described the cognitive dysfunction seen in schizophrenia as a failure to produce the appropriate response as a consequence of an impaired ability to represent, maintain or apply task-setting information; a process that is thought to rely on intact function of the prefrontal cortex. Consequently, the deficits in cognitive performance should be particularly evident when task-setting cues dictate when different responses are required to the same stimuli.

Paradigm description. Conditional discrimination paradigms may be used to assess the way in which task-setting cues can control performance. In these tasks, participants are required to learn associations between arbitrary pairs of stimuli, or between arbitrary stimuli and responses (e.g. Petrides, 1985). These associations are learned by trial-and-error and based on feedback, either from the experimenter in human studies or food reinforcement in animal studies. In a conditional discrimination task, the performance of a particular response may be appropriate in the presence of a specific cue but is inappropriate at other times. For example, participants may learn that in the presence of A, response X (but not Y) is

required, whereas in the presence of B, Y (but not X) is required. In biconditional discrimination tasks, correct responses are dictated by the particular combination of cues, usually represented by AX+, BX-, AY-, BY+, where A, B, X, Y represent cues, and '+' and '-' respectively represent the presence and absence of appropriate outcomes.

Validity. There have been few studies in humans. A pilot study using an allergy prediction task (Aitken et al., 2000), found patients learned the conditional discrimination less rapidly than controls (unpublished) and similar findings occurred in high versus low schizotypes (Haddon et al., 2011). Glutamatergic and dopaminergic drug effects have been reported in animals but it remains to be seen if they are reproducible in humans (Dunn and Killcross, 2006).

Perception: signal detection task

The cognitive mechanisms which underpin auditory hallucinations may be an extension of normal cognitive processes (Bentall, 1990). The use of healthy volunteer proxies for hallucinatory phenomena such as inner and imagined speech have been used in functional imaging studies (Shergill et al., 2000; Simons et al., 2009). However, the use of a behavioural task which permits the identification of the cognitive mechanisms underpinning a propensity towards hallucinations would be most time and cost efficient as a biomarker for this symptom. The signal detection task (SDT) (Barkus et al., 2007) aims to objectively determine proneness to auditory hallucinations without using suggestion (Cahill, 1996; Young et al., 1987).

Paradigm description. Participants are asked to indicate whether they hear a voice during brief periods of white noise. There is a voice in 60% of the trials. A third of the voice presentations are clearly audible while the remainder are at auditory threshold. The clearly audible voices give participants an indication of what to expect and those presented at auditory threshold allow for some perceptions to be ambiguous. From these data four pieces of information are provided (e.g. Green and Swets, 1966; McNichol, 1972): hits (a voice is present and participants report hearing it); misses (a voice is present but participants do not report hearing it); correct rejections (a voice is not present and the participants do not report hearing it); and false alarms (a voice is not present but the participant reports hearing it), which is the putative measure of hallucinatory proneness. Measures of sensitivity, specificity and response bias can be calculated using signal detection theory.

Construct validity. In a small fMRI study, Barkus et al. (2007) reported that false perceptions (when compared to hearing a voice which was presented) activated closely similar areas to those associated with hallucinations in patients with psychosis (e.g. Simons et al., 2009) including the inferior and superior temporal gyri and the cingulate. Also, a specific association between positive response bias and hallucinatory proneness items, rather than items relating to visual or

thought intrusions into cognition, was reported (Varese et al., 2010).

Criterion validity

Patients, relatives and high schizotypes. A tendency to report false alarms has been reported in patients with psychosis who report hallucinations (Bentall et al., 1991; Bentall and Slade, 1985). A similar pattern has been observed in healthy volunteers in association with high scores on questionnaire ratings of hallucinatory proneness or positive schizotypy (Barkus et al., 2007; Bentall and Slade, 1985; Rankin and O'Carroll, 1995). Most of these studies report that this tendency exists in the absence of any difference in the ability to detect a signal, although this is not a consistent finding (e.g. Boecker et al., 2000). In addition performance on the SDT also seems to be mediated by age and positive schizotypy in a manner consistent with psychosis risk, that is, younger participants score higher on positive schizotypy, reporting more false perceptions than older participants (Barkus et al., 2011).

Drug-validation studies would be of considerable interest but have yet to be carried out. Given the focus of this task on auditory hallucinations samples in these studies should be recruited on the basis of a propensity towards these symptoms.

Cortical electrophysiology: early sensory event-related potentials

A number of studies suggest that schizophrenia is associated with impaired visual sensory perception: deficits have been demonstrated in motion, contrast sensitivity and spatial discrimination (Javitt, 2009). Event-related potentials (ERPs) recorded by electroencephalography have the temporal resolution necessary to identify the neural basis and are potential biomarkers of early sensory processing. Two promising measures of early sensory processing have been developed in the auditory and visual modalities, namely mismatch-negativity (MMN) and P1 potentials. The MMN potential is a negative ERP wave peaking over the temporal cortical lobes at 150–200 ms post-stimulus in response to auditory stimuli that deviate from an established pattern (Näätänen et al., 1978). The visual P1 potential is generated by any perceived visual stimulus. It peaks between 100 ms and 150 ms and has a bilateral occipital distribution (Di Russo et al., 2003).

Paradigm description. MMN tasks involve participants listening to repetitive sound patterns which are infrequently interrupted by stimuli that deviate in terms of intensity or duration (Michie, 2001). The process is attention-independent and the participants are usually instructed to ignore the sounds while watching a film or reading a book. The visual P1 wave is typically evoked by watching a black and white checkerboard pattern repetitively flashed on a screen. The participants are instructed to ignore these stimuli but are visually engaged by an attentional task (e.g. pressing a button whenever an animal appears on the screen) (e.g. Yeap et al., 2006). In the case of both P1 and MMN the outcome measure

is the peak amplitude or the mean amplitude of a window centred on the peak of interest.

Construct validity. Functional imaging studies have provided evidence for reduced activation during perception in both visual and auditory cortex of patients with schizophrenia. In the case of MMN, a combined MEG/fMRI study demonstrated reduced activity planum temporale (secondary auditory cortex), an area proposed to be crucial for integration of auditory stimuli (Kircher et al., 2004). A combined EEG/fMRI study of early visual potentials in schizophrenia found reduced activation of the V1 and V2 visual areas (Martinez et al., 2008). Moreover, the P1 potential is predictive of performance on cognitive tasks that require visual encoding (Butler et al., 2009; Haenschel et al., 2007). This has been interpreted as evidence that inefficient encoding contributes to higher-order cognitive deficits. Similarly, the MMN abnormalities in schizophrenia predict social and occupational impairment (Light and Braff, 2005).

Criterion validity

Patients, relatives and high schizotypes. MMN is reliably reduced both in patients (Umbricht and Krljes, 2005) and at-risk individuals, including unaffected relatives (Michie et al., 2000), schizotypal individuals (Niznikiewicz et al., 2009) and children at-risk for schizophrenia (Bar-Haim et al., 2003). In the visual domain, the P1 potential has been consistently shown to be of reduced amplitude in patients (Doniger et al., 2002; Foxe et al., 2005; Schechter et al., 2005; Yeap et al., 2006), unaffected relatives (Yeap et al., 2006) and, recently, in high schizotypes (Koychev et al., 2010).

Glutamate challenges. Ketamine challenge in healthy volunteers led to diminished MMN amplitude (Kreitschmann-Andermahr et al., 2001; Oranje et al., 2000; Umbricht et al., 2000). No studies of ketamine on visual P1 amplitude in healthy volunteers have been published but animal data suggests that ketamine may disrupt the neural mechanisms of sensory information processing (Heggelund and Hartveit, 1990; Kwon et al., 1991).

Predictive validity

Dopamine antagonists. Treatment with typical or newer antipsychotic drugs has no effect on the MMN abnormality in patients (Korostenskaja et al., 2005; Schall et al., 1999). Also, unmedicated and recent-onset patients have a pattern of MMN and P1 abnormalities similar to these of chronically medicated patients (Javitt et al., 2000; Umbricht et al., 2006; Yeap et al., 2008b). Finally, an analysis showed that there is no relationship between antipsychotic dosage or duration of treatment and the severity of the P1 potential abnormality (Yeap et al., 2008a).

Dopamine agonists. There have been no studies on the effects of acute dopamine agonist challenge in auditory MMN or P1 ERPs.

Other agents. Benzodiazepine treatment in patients with schizophrenia does not alter the MMN deficits (Kasai et al., 2002).

Cortical electrophysiology: oscillation and coherence biomarkers

Recent theories attribute the core dysfunction in schizophrenia to impaired connectivity between and within brain regions (Andreassen, 1999; Friston, 2005). The synchrony and coherence of neural oscillations is thought to be a fundamental mechanism that enables coordinated brain activity. EEG measures of these processes are therefore a natural target for schizophrenia research (Fries, 2009). Oscillatory activity has been divided into low (omega 1–3 Hz; theta 4–7 Hz; alpha 8–12 Hz) and high (beta 13–30 Hz; gamma 30–200 Hz) frequency bands, a distinction which is thought to reflect different aspects of cortical connectivity (Buzsaki, 2006). However, there is considerable overlap, and the classical cut-offs between bands are somewhat arbitrary (for reviews see Uhlhaas et al., 2008; Uhlhaas and Singer, 2010). The oscillations can be characterized in terms of their power and the degree to which their phases coincide between trials (phase-locking factor) or electrodes (coherence). Also, two types of oscillations are analysed: time-locked (evoked) and non-time-locked (induced). Evoked oscillations are hypothesized to represent perceptual binding, while induced ones underlie cognitive processes (Buzsaki, 2006).

Task description. Neural oscillations are studied using event-related designs in EEG. Any task that evokes a repeated uniform cognitive response can be used to probe connectivity in schizophrenia. WM, perceptual binding and pattern deviance tasks have been employed in both visual and auditory domains to study connectivity in schizophrenia.

Construct validity. A number of experiments have demonstrated a close link between synchronized oscillatory activity and the preparation, initiation and maintenance of cognitive and behavioural acts (Varela et al., 2001). Studies in patients have found that reduced evoked oscillations in the beta and gamma ranges predict WM impairment on a matching to sample task (Haenschel et al., 2009). Similarly, the disruptions of the non-time-locked (induced) gamma oscillations have been linked to impaired performance on several cognitive tasks, suggesting that the neural processes underlying both induced and evoked oscillatory activity are critical to higher order cognitive processes (Basar-Eroglu et al., 2007; Cho et al., 2006).

Criterion validity

Patients, relatives and high schizotypes. Abnormalities of the gamma, beta and alpha oscillations are well documented in patients with schizophrenia (Uhlhaas et al., 2008). Evoked gamma bursts time-locked to auditory and visual stimulation show reduced power and degree of synchronization in

patients (Haenschel et al., 2009; Spencer et al., 2008; Uhlhaas and Singer, 2006) and unaffected relatives (Tsai et al., 2004). In a recently completed analysis, power and phase abnormalities were found in a sample of schizotypal individuals (Koychev et al., 2011). The pathogenesis of the observed oscillatory abnormalities has been attributed to dysfunction within local GABA inhibitory networks that set the rhythm within neuronal networks, and are deficits in the glutamatergic system which mediates long-distance synchronization and/or demyelination that affects the cortico-cortical and cortico-subcortical connectivity (Uhlhaas et al., 2008).

Glutamate antagonist challenges. A study using ketamine in a gating auditory paradigm found augmented gamma and reduced theta response in healthy volunteers (Hong et al., 2009).

Predictive validity

Dopamine antagonists. Data on modulation of oscillatory activity by antipsychotic drugs are limited, with one group reporting reduced gamma activity in patients treated with atypical antipsychotics (Mayner et al., 2008). However, no correlation was found between chlorpromazine equivalents and amplitude of evoked and induced oscillations in patient samples (Haenschel et al., 2009). Also, gamma band abnormalities have been reported in unmedicated patients (Gallinat et al., 2004).

Dopamine antagonists and other agents. There are currently no data on the effect of dopamine agonists or other psychoactive compounds on neural oscillations in humans.

Oculomotor control: saccadic eye movements

The study of eye movements has received much interest in the validation of potential biomarkers due to findings of various oculomotor deficits in schizophrenia. The saccadic eye movements (rapid eye movements that allow the fixation of a new object that has appeared in the visual field) are some of the most widely studied measures in the context of schizophrenia.

Paradigm description. In the prosaccade task a novel visual target appears in the periphery and the participants have to direct their gaze at it. In the antisaccade task the participants have to inhibit the prosaccadic response to a new stimulus and instead look at its mirror image location on the opposite side of the screen. The performance measures of the task are the number of error prosaccades, the latency and the spatial accuracy of the mirror antisaccade.

Construct validity. Imaging studies have demonstrated that the antisaccade is a complex task activating a dorsal frontoparietal cortical network as well as subcortical project targets; specifically, dorsolateral and ventrolateral prefrontal cortex, frontal and supplementary eye fields, the intraparietal sulcus,

striatum, and thalamus are involved (Munoz and Everling, 2004). Evidence from structural and functional imaging studies indicate that the structures underlying the abnormality in schizophrenia are the frontal cortex (Ettinger et al., 2004) and the striatum (Raemaekers et al., 2002). Performance on the task has been demonstrated to have high temporal stability (Ettinger et al., 2003a). Also, the antisaccade error rate correlates with the measures of executive function in patients with schizophrenia (Hutton et al., 2004).

Criterion validity

Patients, relatives and high schizotypes. Patients with schizophrenia have been shown to have normal performance on the prosaccade task (Haraldsson et al., 2008), although some reports suggest decreased latencies of the responses (Reilly et al., 2008). In the antisaccade task, however, they are consistently impaired, making significantly more errors, having slower antisaccade latencies, and showing deficits in calculating the spatial location of the mirror image (Fukushima et al., 1988; Hutton and Ettinger, 2006). Unaffected biological relatives and schizotypal individuals also show impaired antisaccade performance (Calkins et al., 2004).

Glutamate antagonist challenges. Ketamine studies in healthy humans have found a decrease in prosaccade velocity and an increase in saccade latency but only non-significant impairments in antisaccade performance (Radant et al., 1998, Weiler et al., 2000). The latter is in contrast to Condy and colleagues who found that ketamine infusions impaired antisaccade performance in non-human primates (Condy et al., 2005). The discrepancy between studies may reflect the different dosages of ketamine that were used.

Predictive validity

Dopamine antagonists. Treatment of patients with schizophrenia with both first and second generation antipsychotics led to a significant decrease in peak saccade velocity in several studies, but without major effects on antisaccade error rate or latency (Muller et al., 1999; Straube et al., 1999). However, switching from first generation neuroleptics to risperidone was related to improved antisaccade performance (Burke and Reveley, 2002). Another longitudinal study showed that risperidone was associated with improvements in antisaccade latency whereas haloperidol was not (Harris et al., 2006). Studies of healthy volunteers have shown dose-dependent decrease in prosaccade peak velocity and either no effects or negative effects on antisaccades (Reilly et al., 2008). These negative effects could be due to the sedating effect of neuroleptics, as benzodiazepines have similar effects in healthy volunteers (de Visser et al., 2003). In fact, a reduction of prosaccade velocity is a highly replicated biomarker of a compound's sedative effects (de Visser et al., 2003).

Dopamine agonists. Methylphenidate and amphetamine have been reported to improve antisaccade performance

(Klein et al., 2002; O'Driscoll et al., 2005; Wonodi et al., 2006). Importantly, beneficial effects of repeated amphetamine administration in the study by Wonodi et al. were seen only in individuals with high levels of schizotypy.

Other agents. Antisaccade performance is also sensitive to the effects of nicotine (Levin et al., 2006; Newhouse et al., 2004). In healthy smokers, nicotine reduces the rate of reflexive errors (Rycroft et al., 2006) and the latency of antisaccades (Ettinger et al., 2009). Healthy non-smokers also show reduced antisaccade latency with nicotine (Rycroft et al., 2007). An fMRI study suggests that the improvements in antisaccade performance with nicotine may be due to enhanced neural efficiency in the frontal cortex (Ettinger et al., 2009). Importantly, nicotine also improves antisaccade performance in schizophrenia (Depatie et al., 2002, Larrison-Faucher et al., 2004). Conversely, procyclidine, a cholinergic antagonist, leads to antisaccade impairments in schizophrenia (Ettinger et al., 2003b).

Oculomotor control: smooth pursuit eye movements

The first reports of the inability of people with schizophrenia to eye-track accurately a swinging pendulum date from 1908 (Diefendorf and Dodge, 1908). About 100 years later, deficits in the smooth pursuit eye movements (SPEMs; slow eye movements that allow the stabilization of a slowly moving target on the retina) are some of the most robust findings in schizophrenia research.

Paradigm description. In the SPEM paradigm, participants have to follow a small visual target moving at a constant velocity without moving their head. The outcome measures include the ratio between the speed of the moving target and the eye movements and the rate of catch-up saccades that bring the image back onto the fovea.

Construct validity. The existing data indicates that SPEMs are executed by a circuit linking the visual, mediotemporal (MT), medial superior temporal (MST), prefrontal and motor regions of the cortex (Newsome et al., 1988). The deficit in schizophrenia spectrum individuals has been attributed largely to dysfunction in frontal (O'Driscoll et al., 1999) and motion sensitive (Lencer et al., 2003) regions. Similar to the antisaccade task, smooth pursuit performance has good temporal stability (Ettinger et al., 2003a).

Criterion validity

Patients, relatives and high schizotypes. Patients with schizophrenia are less able to follow the target accurately than healthy controls (i.e. they show reduced pursuit gain and make more catch-up and intrusive saccades) (Campion et al., 1992; Ross et al., 2002; Trillenber et al., 2004). Studies in relatives have found similar deficits in gain (Ross et al., 2002) and intrusive saccades (Rosenberg et al., 1997; Ross et al., 2002). Schizotypal individuals have also

been demonstrated to have smooth pursuit abnormalities (O'Driscoll et al., 1998; Smyrnis et al., 2007).

Glutamate antagonist challenges. Ketamine challenge studies have found a range of abnormalities, namely a dose-dependent nystagmus (Radant et al., 1998), increase in the number of anticipatory saccades (Avila et al., 2002) and deficit in measures that test retinal (but not extraretinal) target processing (Weiler et al., 2000).

Predictive validity

Dopamine antagonists. Initiation of antipsychotic treatment has been reported to be associated with a decrease of pursuit gain, indicating a sensorimotor impairment (Lencer et al., 2008). Chronic treatment appears to have a similar effect, as long-term medicated patients perform worse than chronic non-medicated and treated first-episode patients (Hutton et al., 2001; Sweeney et al., 1999; but see Thaker et al., 1999). A study administering low doses of haloperidol, amphetamine and placebo in a sample of healthy volunteers reported an increase in saccadic intrusions during smooth pursuit with the haloperidol that was not present in the other groups (Malaspina et al., 1994). Similar to the antisaccade data, the observed effects could at least partly be attributed to the sedating action of antipsychotics, as benzodiazepines have been shown to decrease SPEM velocity in healthy volunteers (Reilly et al., 2008). Also, evidence from healthy volunteer and schizophrenia studies indicates that nicotine improves SPEM performance (Domino et al., 1997) and the anticholinergic compound procyclidine worsens SPEM performance in schizophrenia (Ettinger et al., 2003b).

Dopamine agonism. In the only currently available study the effects of acute amphetamine on SPEMs, no significant effect of the challenge was reported (Malaspina et al., 1994).

Discussion

We have reviewed several cognitive and physiological biomarkers for schizophrenia for their potential as biomarkers for drug discovery in healthy volunteers. Several conclusions can be drawn on the basis of this literature.

Reliability

The MATRICS initiative stands out in terms of demonstrating reliability – that the same results in terms of group differences and correlations with outcome are seen in different centres and across time (Nuechterlein et al., 2008). This has been driven by the need to find drugs that improve the cognitive deficits of schizophrenia and to convince licensing authorities and Industry of the validity of MATRICS tests as markers of efficacy. There have been no other systematic studies of reliability of the other biomarkers reviewed.

Surrogate populations

Many of the biomarkers show differences between controls and criterion groups – patients, unaffected relatives and schizotypal individuals. The lack of institutionalization, chronic disease and medication in the healthy volunteer groups confirms the idea that the abnormalities observed in schizophrenia are not due to the confounding factors of illness course and treatment. Instead, it indicates that cognitive dysfunction is a core feature of schizophrenia that is present across the disease spectrum (Heinrichs, 2005). Familial abnormalities suggest the measures are endophenotypic trait biomarkers. This is not weakened if the biomarkers are also abnormal in schizotypal individuals since they may also carry risk genes (e.g. Fanous and Kendler, 2004). Equally, however, unaffected family members may have schizotypal features – this is rarely checked in the literature – so familiarity may involve an element of state-dependency (see Diwadkar et al., 2006 for effects of familial risk and schizotypy interacting with age for WM performance).

Ketamine as a pharmacological model of schizophrenia

The available data suggests that acute ketamine administration has a generally mild disruptive effect on neurocognitive function in humans. The pattern of abnormalities has similarities to those observed in patients, relatives and high schizotypes (Krystal et al., 1999). It has been argued that the cognitive effects of ketamine and the symptoms it evokes may more closely mimic deficit symptoms and cognitive impairment in schizophrenia (Pomarol-Clotet et al., 2006) and this would be in keeping with the lack of effect of haloperidol or clozapine on these phenomena. That ketamine also mimics some of the GABA/glutamate neurochemical abnormalities of schizophrenia suggests that ketamine-evoked biomarker changes in volunteers have significant construct validity.

Dopamine and cognition

Sensitivity to drug challenges aimed at improving cognition or clinical states was evident with several of the reviewed biomarkers. The most consistent finding was that dopaminergic treatments generally affect cognitive performance. An important characteristic is that enhancing dopamine function tends to selectively improve low baseline performance but worsen optimal performance. These findings fit in well with the idea that executive problems in schizophrenia spectrum disorders are due to suboptimal dopamine activity. Some authors have proposed a U-shaped curve to describe the relationship between dopamine and executive function, with hypo- and hyperdopaminergic states leading to cognitive abnormalities (Barch, 2004). The proposed suboptimal dopamine function in the schizophrenia-spectrum has been attributed to the high activity version (val/val genotype) of the enzyme that metabolizes dopamine, namely catechol-O-methyl transferase (COMT). In support of this, tolcapone, an inhibitor of COMT, improved N-back performance in healthy volunteers at high loads (Mattay et al., 2000). Also, participants with the val/val genotype benefited preferentially

from treatment with tolcapone in an episodic memory task. In a different study, low WM performance in val/val participants was improved by a challenge with dextroamphetamine. The same agent led to deterioration at high WM capacity in participants with the met/met genotype (Fava et al., 1999). Abnormalities in other enzymes involved in clearing dopamine from the synaptic cleft have also been implicated, but evidence for direct involvement in schizophrenia spectrum pathophysiology is scarce (Apud and Weinberger, 2006). A second important feature of dopamine effects is that D1 agonists appear to be more effective than D2 agonists, and this may reflect the greater concentration of D1 receptors compared with D2 receptors in the prefrontal cortex. The implication of these findings is that frontal dopamine neurotransmission is a validated target for future drug development and a promising line of development.

Also, the improvement of some of the biomarkers by compounds affecting non-dopamine neurotransmitter systems in healthy volunteers (such as the benefit to eye-tracking performance by cholinergic agonists) suggest that cognitive processes may have a variety of neuromodulatory influences, so possible drug targets are not limited to the most commonly explored dopaminergic and glutamatergic systems.

State and trait biomarkers

The reviewed literature showed a variable relationship between clinical state and biomarker performance; some biomarkers showed a degree of state dependency whereas others did not. The state-dependent biomarkers included salience attribution, eye-tracking and perhaps WM tasks where there is some evidence for varying degrees of improvement with atypical antipsychotics. This effect could be due to their lower affinity for the D2 receptor, which may permit endogenous dopamine activity (Kapur and Remington, 2001). This might be particularly important for prefrontal cortical function, and the performance on tasks that depend on its integrity, such as WM and eye-tracking, reflects this. In support of this, no improvement is found with typical antipsychotics, despite their efficacy in controlling positive symptoms. The practical implication of such biomarkers is that they could potentially be validated as clinical end-points to assess efficacy of agents that ameliorate both cognitive impairment and psychosis.

Measures such as early sensory event-related potentials and oscillations were generally not influenced by antipsychotic treatment or clinical state. This indicates that the underlying abnormality is probably state-independent and related to factors predisposing to schizophrenia. Findings of similar abnormalities in individuals at genetic or psychopathological risk for schizophrenia support this. ERPs and oscillatory synchrony and coherence can be informative about neural connectivity, dysfunction in which has been argued to be a core feature of schizophrenia. In other words the biomarkers relate to a neural process implicated in pathogenesis and so have some construct validity. Using such measures as biomarkers in drug development would be most useful in assessing novel agents that aim to modify the disease process through regulating connectivity. They have no use in detecting drugs that are variations on

existing antipsychotic drugs with action on dopamine. There is as yet little information about drug effects on EEG measures and this is an important priority for future research.

The state/trait distinction is not cut and dried. For example, despite the modest data suggesting improvement of WM and eye-tracking performance with atypical antipsychotic treatment, these deficits are still found in first-degree relatives. This indicates that they are at least to a certain extent independent from clinical state and are likely to persist in a milder form even when complete remission is achieved. Trait biomarkers have the potential to detect drugs that prevent onset of psychosis by acting on mechanisms of vulnerability that may be distinct from mechanisms of the symptomatic state.

Some studies suggest that biomarkers in the proposed target groups may have predictive utility for drug development. For example, McClure et al. (2010) showed that pergolide improved visual-spatial WM in a small sample of 25 people with Schizotypal Personality Disorder (diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)) when given for a short period of 4 weeks. This cognitive benefit was also associated with symptomatic improvement.

Future directions

One of the clear priorities of future research is the development of non-dopaminergic agents that are effective in treating the cognitive and psychotic features of schizophrenia. As argued previously, the proposed biomarkers can assist in this endeavour by allowing early proof-of-concept studies in surrogate populations. However, as the spectrum of clinical efficacy of such compounds emerges they will help to validate biomarkers for drugs targeting different aspects of schizophrenia.

There is a clear need for more data on the reliability of the measures especially for the non-MATRICES biomarkers and for data about drug actions on the novel biomarkers (SDT, SAT) and the EEG measures. Further, standardized procedures need to be agreed on and established in each task. These are all key prerequisites in order for large, multi-site screening of novel compounds to take place.

Further validation of biomarkers can be achieved through prospective clinical trials in target groups such as unaffected relatives and high schizotypes. For example, McClure and colleagues show that such design can give a more clinically relevant picture of the properties of the drug and the biomarker than the trials where acute drug administration takes place (McClure et al., 2010).

From the basic science point of view, more research is needed into the pathophysiology of the cognitive mechanisms that underlie the biomarkers. Dissecting the neurophysiological and molecular bases of the different components of complex functions such as WM could reveal a number of prospective targets for drug development. Such informed approach to research and development will benefit from the possibility for quick validation of the resulting compound with the biomarker that they were derived from (in this case, WM).

Finally, imaging techniques such as fMRI and PET are an exciting field for cognitive biomarker research. However, more research is needed to identify reliable and pathophysiologically relevant outcome measures that will be useful in the settings of a clinical trial.

Funding

The preparation and the work surrounding this article has been carried out with a grant from Plvital Ltd.

Conflict of interest

Ivan Koychev has been awarded a Manchester Strategic PhD Studentship, sponsored by the University of Manchester and Plvital Ltd. Emma Barkus acknowledges the support of a Young Investigator Award from NARSAD. Ulrich Ettinger is supported by DFG grant ET 31/2-1. Jonathan P Roiser is a consultant for Cambridge Cognition and has received support from St Jude Medical for conference attendance. John Francis William Deakin has carried out paid consultancy work and speaking engagements for Servier, Merck Sharpe and Dohme, Astrazeneca, Janssen, and Eli Lilly. The fees are paid to the University of Manchester to reimburse them for the time taken. John Francis William Deakin, Simon Killcross and Lawrence Wilkinson own shares in Plvital Ltd.

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