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Relating constructs of attention and working memory to social withdrawal in Alzheimer's disease and schizophrenia: issues regarding paradigm selection

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ABSTRACT

Central nervous system diseases are not currently diagnosed based on knowledge of biological mechanisms underlying their symptoms. Greater understanding may be offered through an agnostic approach to traditional disease categories, where learning more about shared biological mechanisms across conditions could potentially reclassify sub-groups of patients to allow realisation of more effective treatments. This review represents the output of the collaborative group "PRISM", tasked with considering assay choices for assessment of attention and working memory in a transdiagnostic cohort of Alzheimer's disease and schizophrenia patients exhibiting symptomatic spectra of social withdrawal. A multidimensional analysis of this nature has not been previously attempted. Nominated assays (continuous performance test III, attention network test, digit symbol substitution, N-back, complex span, spatial navigation in a virtual environment) reflected a necessary compromise between the need for broad assessment of the neuropsychological constructs in question with several pragmatic criteria: patient burden, compatibility with neurophysiologic measures and availability of preclinical homologues.

1. Introduction

Diagnosis of central nervous system (CNS) disorder is still heavily based upon expert subjective judgement. Neuropsychiatric disorders such as schizophrenia or major depression remain solely defined and categorized based on interpretation of sets of observed symptoms (American Psychiatric Association, 2013). Although the predominant neurological disorders (i.e. Alzheimer's and Parkinson's disease) can be objectively diagnosed by defining protein pathologies, at present this tends to only occur *post-mortem*. In-life diagnosis again depends upon interpretation of symptoms and remains probable until histopathological confirmation. Critically, none of the major CNS diseases are defined and diagnosed based on an understanding of the biological mechanisms underlying the symptoms. This may well be hindering the identification of more effective treatment strategies for afflicted individuals.

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Further investigation into different ways to think about and potentially redefine traditionally defined diseases is warranted (Insel et al., 2010). Potential systems of objective biological disease classification need to consider that there may be a disconnect between superficially overlapping symptoms and aberrant neurobiological substrates. A good example of this lies in the case of symptoms of social withdrawal. Social withdrawal is often present as an early sign in a number of neuropsychiatric disorders, is a major determinant of prognosis and an important source of the indirect cost of these diseases to society (Department for Work and Pensions, 2013). Social withdrawal is also frequently observed as neurological disorders progressively worsen. There are no approved biological treatments for social withdrawal in any disease. Symptoms of social withdrawal have been shown to be at least partially independent from other symptoms in Alzheimer's disease and schizophrenia, which may point to the potential for an as yet undescribed common neurobiological substrate linking these symptoms between each disease (Porcelli et al., 2018, this issue). However, there are clearly a multitude of potential causative biological mechanisms by which social withdrawal may arise. To date, the comparative study of social withdrawal across disease states has been poorly studied and the scales of assessment remain comparatively underdeveloped.

Using the above as a starting point, a European Union funded Innovative Medicines Initiative research project call was launched at the beginning of 2016: PRISM (**P**sychiatric **R**atings using **I**ntermediate **S**tratified **M**arkers). PRISM was inspired by previous efforts such as the NIMH-funded Research Domains Criteria (RDoC) (Insel et al., 2010; Kas et al., 2017). The specific aim of PRISM is to re-assess patients diagnosed with disorders of known differing pathophysiology, namely Alzheimer's disease (AD) and schizophrenia (SCZ), and investigate whether neurobiological substrates causing social withdrawal remain true to traditional diagnostic boundaries or can redefine patient groups in different ways. To achieve this, PRISM aims to deploy a broad phenotypic battery to assess AD and SCZ patients exhibiting high and low social withdrawal in comparison to age matched healthy controls. An important first objective of PRISM was to review the potential test components that could be included, as efficient design of the phenotypic battery is key to the success of the project. Within the area of cognition three domains, namely sensory processing, attention, and working memory emerged as being potentially pivotal to the expression of social withdrawal. Although other cognitive domains may also modulate social functioning (Bell et al., 2009), these three were selected primarily because of the relative extent of:

1) Evidence that these domains may modulate social functioning in healthy controls (Bowie et al., 2008; Vlamings et al., 2010; Cacioppo & Hawkley, 2009).

2) Evidence of impairments in these domains in both diseases (Jahshan et al., 2012). There exist a number of excellent reviews addressing aspects of cognitive dysfunction in AD or SCZ along with other allied disorders (Finke et al., 2013; Huntley & Howard, 2010; Keefe & Harvey, 2012; Kessels et al., 2011; Lett et al., 2014; Morris & Baddeley, 1988; Weintraub et al., 2012).

3) Potential for reverse translation into animal models (Wallace et al., 2015), to facilitate further dissection of their neurobiological bases.

The PRISM project exemplifies the elaboration of strategy that underpins a practical undertaking of an RDoc style reclassification approach to CNS disease. The novelty of this work lies in the assessment of the holistic evidence across disease states that justifies not only the exploration of social withdrawal as an overlapping symptom, but the choice of the three cognitive domains that may help to elucidate neurobiological substrates. The review will also assess the tools that are available to probe these domains and the potential strengths and weaknesses when they are deployed in a complex cohort of AD and SCZ patients of high and low socially withdrawn status. If a quantitative biological insight into social withdrawal can be derived from these patients, it is of vital importance that these findings can stimulate back-translation into pre-clinical research. The final facet of the review will consider how the chosen clinical tools could be translated into pre-clinical tasks. Note that within this issue there are a number of supporting papers that provide greater in depth review of the psychobiology of social withdrawal (Porcelli et al., 2018, this issue), the role of sensory processing (Danjou et al., 2018, this issue) and the challenges of assembling a clinical battery to include imaging, electrophysiology, cognition, smart phone passive monitoring and traditional clinical assessment suitable for this range of subjects (Bilderbeck et al., 2018, this issue). This review, along with the others in this issue, are therefore unusual in that the aim is both academic and pragmatic. The need is to understand the subject matter across several dimensions; cross-symptomatic, trans-pathologic, and the potential for translation. Only if success can be achieved across these three planes can a fundamentally better understanding of the biology involved be achieved. If this is possible then the potential for improved diagnosis, deployment of existing therapeutics and the development of novel ones be effectively facilitated.

2. Concepts of attention and working memory in humans

2.1. Psychological Substrates

> "Everyone knows what attention is" William James, 1890, The Principles of Psychology

Most people would profess to an experiential understanding of the concepts of "attention" and "working memory" through the performance of everyday tasks, for example remembering a phone number to dial, following a recipe, getting dressed, completing basic mental arithmetic, or navigating complex street directions. These common human experiences are underpinned by complex psychological constructs that theorists have described in a number of different ways (e.g., Carrasco, 2011; Carretie, 2014; Cowan, 2008; Haladjian & Montemayor, 2015; Luck & Gold, 2008; Postle, 2006). The exact distinction between processes of attention and working memory can be somewhat ambiguous, and the scope of each term has evolved over many decades of research (e.g., Engle, 2018; Kane et al., 2001; Kiyonaga & Egner, 2013; Kreitz et al., 2015). Often researchers use different but related terms, for example "short-term memory", "executive attention", or "sustained attention", when describing these closely associated substrates (Richardson, 2007).

In this manuscript, attention was broadly defined as: *"the selective filtering of perceptual information"* (after Haladjian & Montemayor, 2015). However, attention can be deconstructed into multiple neuropsychological and/or clinical processes, each with potentially dissociable neurobiological and neuronal substrates. For instance, widely described sub-components of attention include reflexive attention, visual orientation, learned orientation, vigilance, habituation, and processes of selective, sustained, and divided attention (Luck & Gold, 2008). Use of variants of the Attention Networks task (Fan et al., 2001; Fan et al., 2002; Fossella et al., 2002) has considerably shaped understanding of the concept of attention (Fan et al., 2003; Pessoa et al., 2003). The investigational model proposed by such work highlights the potential importance of three attentional networks: the executive-control network, the alerting network, and the orienting network (Posner, 1996). Briefly, the orienting network is involved in adjusting the position of the organism (or its sensory apparatus) to maximize input of sensory information. The alerting network is responsible for obtaining and maintaining an alert state, and the executive-control network is involved in error detection and resolving conflict between competing areas of the brain that might be simultaneously active during these processes (Fan et al., 2003; Fan & Posner, 2004; Pessoa et al., 2003; Rueda et al., 2005a). Altogether, depending on the objectives of the experimenter, there may therefore be several ways in which to parse

attentional processing into more finely detailed subcomponents, not all of which may complement each other perfectly.

Working memory represents a specific subset of the processes encompassed by attention. For the purposes of this manuscript, working memory was defined as: "*the short term maintenance and manipulation of information in the absence of sensory input*" (after Eriksson et al., 2015). This definition efficiently posits some key attributes: that it is temporary in nature (or susceptible to interference from other demands), that representations are subject to flexible processing related to the goal, and that this can happen completely internally without the need for continued external stimulation. Another key defining feature of working memory is that it displays capacity limitation (Broadbent, 1975; Cowan, 2001; Miller, 1994). Thus, for many different types of representations across a variety of categories (e.g. words, numbers, objects, sounds), working memory is a process by which, for a short time at least, these representations have greater access to a variety of operational transformations. However, alternative accounts of resource limitation in working memory suggest that working memory capacity is not defined by an absolute number, but rather is a limited resource that has to be divided between all of the items to process (Ma et al., 2014). Thereby, the greater the quality of detail that needs to be remembered for an item, the less of such items can be held and manipulated in working memory. It is well known that there can be large differences in both attentional performance and working memory capacity across individuals (Kane & Engle, 2002; Luck & Vogel, 2013; Stormer et al., 2013; Strauss et al., 2014). Performance will also naturally vary as a function of age. For example, as a core cognitive trait of an individual, working memory performance remains fairly stable over the 20 to 50 years age period then begins to linearly decline after this point (Lufi et al., 2015; Nyberg et al., 2012).

Given such broad and heterogeneous constructs, moving from psychological theory to a clinical phenotypic battery requires some thought as to;

1) which aspects of attention and working memory are most important to consider to meet the objectives of the experiment
2) the suitability of assessment tools available to measure these aspects in the intended patient populations
3) the potential for measurement tools to be deployed either in a MRI scanner and/or during EEG assessment
4) the applicability of the chosen tools for accurate reverse translation into the preclinical context

To begin addressing this, the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) initiative has already considered exactly this from a translational cognitive neuroscience perspective, attempting to define what psychological constructs were amenable to measurement in a clinical psychiatric context for the study of schizophrenia (Barch & Smith, 2008, Barch et al., 2009b). Amongst other psychological processes, CNTRICS considered several distinct aspects of attention and working memory ("goal maintenance", "flexible updating", "interference control" and "capacity limitation") to be immediately amenable to measurement in a clinical environment and also likely relevant to their disease in question. The group then nominated key assays that they felt would be most appropriate for use in each of these domains, both clinically (Nuechterlein et al., 2009; Barch et al., 2009a) and preclinically (Lustig et al., 2013;, Dudchenko et al., 2013), and also with awareness of the increasing need to incorporate biomarkers into drug discovery focused work (Luck et al., 2012;, Barch et al., 2012). Such work has been hugely influential for many different researchers, including the PRISM consortium. Indeed, the ability to test the subcomponents of attention and working memory as described above has been carefully considered during the PRISM task selection process. Although the boundaries between the theoretical constructs of attention and working memory can often be ambiguous, their dissection into more precise neuropsychological subcomponents is very tenable, and may offer great promise when studied across diseases to understand the substrates causing impairment in different clinical populations.

2.2. Neurobiological Substrates

Consideration of what attention and working memory is, and how it can be broken down into different measurable neuropsychological aspects, naturally leads to questions as to which regions or networks in the brain may subsume these processes. The use of human imaging and electrophysiological approaches are now assisting in identifying the neural networks and activities that underlie the functional subtypes of attention and working memory (Driver & Frackowiak, 2001; Kastner and Ungerleider, 2000; Pessoa et al., 2003). If these substrates can be accurately described in a small range of assays then effective back translation to homologous processes in animals becomes an attainable goal.

Current understanding of the neuronal substrates that mediate attention comes predominantly from experimental tasks using visual processing and, to a lesser extent, other sensory modalities such as auditory processing. As previously mentioned, work with the Attention Networks Task has proved very informative in linking defined brain regions with different aspects of attentional processing. For instance, the alerting network is composed of thalamic areas, locus coeruleus, and cortical areas including frontal and parietal structures (Posner, 2008). The orienting network is comprised of sensory systems including the frontal eye fields and both superior and inferior parietal lobes (Posner, 2016). Connectivity between the left and right parietal lobes is fundamental in orienting to relevant stimuli. The orienting network plays a dominant role in guiding attention in early childhood (Petersen & Posner, 2012; Rueda et al., 2004) to be replaced progressively from approximately 4 years of age by the executive-control network (Posner & Rothbart, 1998; Rothbart et al., 2003; Rothbart & Posner, 2005; Rueda et al., 2004; Rueda et al., 2005b). The principal components of the executive-control network include the anterior cingulate and lateral frontal cortex, which receive inputs from areas that underlie emotional regulation such as the anterior insula and the ventral tegmental area. Thereby these frontal areas, through their extensive connections with reward and motor control systems, exert strong influences on attentional signals and the attentional modulation of motor output.

Proponents of the "Component Process" model of working memory (Baddeley and Hitch, 1974; Markowitz et al., 2015; Repovs & Baddeley, 2006) draw attention to the fact that, in the most general sense, no processes should be considered unique or specific to working memory (Christophel et al., 2017). Different processes, and thereby brain regions, will be recruited depending on what type of items are being maintained, how they are to be manipulated, and what further processing has then to be taken following this manipulation. That is not to say, however, that some brain regions and networks may play a more central role than others in specific aspects of working memory. For example, both the prefrontal cortex (particularly dorsolateral prefrontal cortex) (Funahashi, 2017) and posterior parietal cortex have been consistently implicated as specific nodes involved in working memory processes, as evidenced from lesion (Muller & Knight, 2006; Tsutsui et al., 2016), electrophysiological (Luria et al., 2016; Rawley & Constantinidis, 2009) and neuroimaging (Barch et al., 2012; Curtis, 2006) studies in man and animals [although see also Mackey et al., 2016 for a contrasting account]. In a similar manner, certain structures and circuits have been implicated as particularly involved with certain subtypes of working memory. The best example here is the involvement of hippocampal – prefrontal connectivity in spatial working memory processes, an activity observed in both human and animal studies (Spellman et al., 2015).

2.3. Neuronal Substrates

Potential neuronal substrates of attention have been delineated in some detail, the most compelling of which describe a "normalization model" of attention (Reynolds & Heeger, 2009). According to this model, attention alters the balance between excitation and inhibition of competing neuronal populations that represent different objects, locations or features (Thiele & Bellgrove, 2018). Firing rates of neuronal populations representing to-be-attended stimuli increase, resulting in suppression of firing rates of competing populations whose representations will not be attended to (Carandini & Heeger, 2011). At the electrophysiological level, these regional effects may contribute to attention-induced changes in oscillatory activity in the gamma frequency range and in lower-frequency bands, such as theta, alpha, and beta frequencies (Thiele & Bellgrove, 2018). The change in gamma frequency range may be associated with increases in inhibitory drive, changes in alpha oscillations with enhanced attentional control, and changes in beta oscillations with feedback influences (Thiele & Bellgrove, 2018). Despite this progress, the exact attentional correlates of these electrophysiological findings in specific brain regions still need to be elucidated.

As well as attention, some progress has been made in determining the potential neuronal substrates of working memory. A very popular approach to this topic has been to utilize "delay" tasks in awake behaving animals whilst recording electrophysiological activity of neurons (Curtis, 2006). Responding during tasks that involve such working memory events typically results in persistent neuronal activity in various brain regions during processing (Curtis & D'Esposito, 2003; Riley & Constantinidis, 2015), suggestive of the fact that this activity may relate to maintenance and/or manipulation of items, although the exact functions of such activity remains under debate (Barak et al., 2010; Curtis & Lee, 2010; Sreenivasan et al., 2014). It is not clear whether such recurrent firing within existing synaptic connections is a sufficient neurophysiological substrate to support working memory, or whether forms of short term synaptic plasticity are also required (Barak & Tsodyks, 2014; Mongillo et al., 2008). It has been suggested that working memory does not necessarily depend upon structural plasticity *per se* (Eriksson et al., 2015).

In the opening section of this review, definitions of both attention and working memory have been established. While these two processes are dissociable to an extent, they are clearly heavily interdependent and possess similarities at several neuropsychological levels. Both processes can engage and utilize many modalities of information (e.g. visual, auditory, olfactory), although attention typically refers to a set of lower level or more fundamental cognitive processes than working memory does. With the requirement for complex interaction and integration between these various neuropsychological processes to generate higher cognitive abilities (e.g. spatial navigation, language, rule learning) it is also clear that there is likely to be significant overlap in the neural substrates involved. The goal of PRISM is to determine whether a deep phenotyping approach can be used to learn more about the determinants of social withdrawal in AD and SCZ, such that patients may be classified differently and treated more effectively. Accordingly, several different threads of evidence need to be considered to justify this approach and then to establish testing protocols. This begins with a consideration of evidence of impairment of attention and working memory in each disease, and the contribution of these psychological processes to normal social behaviour. Most importantly, the confluence of these lines of evidence needs to be considered, i.e. what evidence exists to suggest that parameters of attention and working memory may be determinants of social withdrawal across each disease.

3. Cognitive impairments in AD and SCZ

3.1. Attention and working memory impairments in AD

Alzheimer's Disease is a progressive neurodegenerative disorder that significantly increases in incidence as a function of advancing age. AD is characterized pathologically and confirmed upon autopsy by the presence of amyloid plaques and neurofibrillary tangles (Hardy and Selkoe, 2002, Perl, 2010, Selkoe and Hardy, 2016, Serrano-Pozo et al., 2011, Wang et al., 2017). Plaques and tangles display stereotypical patterns of expression and potential propagation in the brain over time as a function of disease severity (Braak and Braak, 1991, Marquie et al., 2017). The pathological burden that an individual patient exhibits likely results in their own unique pattern of symptoms (Landau et al., 2012). Symptomatically, AD is most well described as a progressive disorder of cognition. Typically, patients will first clinically present with complaints of disturbance of episodic or autobiographical memory (Burns and Iliffe, 2009), what might be considered the canonical in-life symptom of probable AD. Over a period of years, AD will then progressively impact nearly every aspect of cognition, until reaching the severest stage where a patient has little ability to engage in any aspect of daily function independently. Although memory disorder is the hallmark symptom of AD, and the disease will eventually impact almost all aspects of mnemonic function, specific impairments in attention or working memory are not a criterion of probable diagnosis (McKhann et al., 1984).

Attention is probably the first non-mnemonic aspect of cognition to be affected by AD (Perry & Hodges, 1999). In fact, poor attentional performance (and related executive function measures) can often better discriminate amnestic mild cognitive impairment from normal aging than tests of memory can (Rapp & Reischies, 2005). Attentional impairments appear before deficits in language and visuospatial functions in AD, possibly accounting for difficulties in daily living observed in early or mild forms of the disease (Pepeu et al., 2013). In mild-to-moderate AD, attentional impairments are observed in more than 80% of subjects (Gauthier et al., 2010). In terms of sub-domains of attention, divided attention and aspects of selective attention (i.e., disengagement and shifting of attention) start to decline first, resulting in difficulties in performing simultaneous tasks (Baddeley et al., 2001, Finke et al., 2013). Sustained attention is relatively preserved, as are aspects of alerting and orienting functions (Zhang et al., 2015), but can frequently be affected in later stages of the disease (Gauthier et al., 2010). Although quantitative attentional impairments can be detected in all forms of dementia, this pattern of impairment seems most characteristic for AD, although not all subjects will fit this profile (Pepeu et al., 2013).

AD patients do not present with a single, simple working memory deficit. Evidence suggests that the degree of working memory impairment observed early in the disease process can predict levels of functional decline over time (Pillai et al., 2014). The degree and quality of working memory impairment measured in AD from its earliest stages may be influenced by comorbidity or by the cognitive subtype of AD under examination. For instance, AD with depressive (Araujo et al., 2014) or psychotic (Koppel et al., 2014) comorbid elements may be associated with relatively greater declines in working memory, although this could reflect a generally broader cognitive impairment in such patients. AD itself is postulated to begin with an extended preclinical phase, potentially of decades or longer (Caselli et al., 2017), which makes it interesting to note a potential gradation of change in working memory function from healthy aging, to mild cognitive impairment, to that observed in AD (Kirova et al., 2015). Using the Component Model as an explanatory framework, several groups have attempted to provide further resolution of the neuropsychological nature of the working memory deficit in AD (as reviewed in Huntley and Howard, 2010, Kessels et al., 2011, Morris and Baddeley, 1988). These reviews suggest that the most impacted aspect of working memory performance in early AD likely lies in the function of the

"central executive system", the hypothetical frontal command system which acts as a master coordinator of subsidiary phonological and visuospatial systems (Baddeley and Hitch, 1974). Along these lines, early AD patients were reported to have more problems with executive control processes of working memory, finding it difficult to perform under conditions when there is competition for attentional demand, for instance during dual task performance or high distractor load (Morris and Baddeley, 1988). The degree by which distractor load is impairing may correlate with the underlying degree of dementia (Corkin and Corkin, 1982). In contrast, working memory span may only be moderately affected during early stages of the disease (Carlesimo et al., 1994, Martin et al., 1985, Perry et al., 2000), and other aspects of function such as recency during free recall and the phonological loop may be essentially spared (Huntley and Howard, 2010). The ability to chunk material to increase working memory span is also relatively spared in early AD (Huntley et al., 2011).

There is certainly some degree of overlap of descriptions of attentional and working memory impairment in AD. At a neural level, commonality in patterns of impairment reflect how AD progressively affects the partially shared networks that subsume each cognitive process. Thereby, early attentional and working memory impairments are likely to be caused by AD pathology in the executive-control network, while areas involved in the alerting and orienting networks are usually preserved until the progression of the disease becomes more severe (Zhang et al., 2015). Of note, a growing body of evidence emphasizes that dysfunctions in connectivity within networks, rather than alterations in specific brain areas, may underlie some of the impairments observed (e.g., Markett et al., 2014). At the neurotransmitter level, deficits in the cholinergic system are well described in AD and could account for a significant component of attentional impairments in these subjects (Schliebs & Arendt, 2011). However, deficits in other neurotransmitter systems, such as dopamine and serotonin amongst others, must also be considered as contributing factors (Lai et al., 2002; Martorana & Koch, 2014).

Altogether, such results are suggestive that the attention and working memory deficits in early AD may be more attributable to a dysfunction in frontal circuitry involved in allocation of attentional and executive control resource during tasks of higher cognitive load. However, such an interpretation is by no means definitive or all-encompassing. Counter to this evidence are reports that AD patients present with a qualitatively different type of working memory impairment than that observed in frontotemporal dementia, a "classic" frontal disease (Bird et al., 2010, Kramer et al., 2013, Leslie et al., 2016, Possin et al., 2013, Stopford et al., 2010, Stopford et al., 2012). It is further argued that there is no straightforward relationship between working memory performance and standard psychological measures of frontal lobe function (Stopford et al., 2012). Further work will be required to resolve these issues.

3.2. Attention and working memory impairments in SCZ

While most commonly associated with symptoms of hallucinations and delusions, SCZ is a heterogeneous disorder that can encompass impairment in cognition, perception, emotion and motivation (Blanchard and Neale, 1994, Green and Nuechterlein, 1999, Heinrichs and Zakzanis, 1998, Oltmanns, 1978). SCZ is often divided into three major categories of symptoms: positive, cognitive and negative symptoms (Kay, 1990, McGlashan and Fenton, 1992, Tandon et al., 2009). Dysregulation of dopaminergic neurotransmission, impacting both subcortical and cortical networks, is regarded as a potential core mechanism of SCZ (Amato et al., 2018, Howes and Kapur, 2009, Kapur and Mamo, 2003, Lau et al., 2013, Winton-Brown et al., 2014). Specific impairments in attention or working memory may be observed in individual patients but neither symptom alone is a necessary or sufficient criterion for the diagnosis of schizophrenia.

Attention is well known to be one of many cognitive domains impacted in SCZ, together with working memory, verbal learning and memory, visual learning and memory, reasoning and problem solving, processing speed and social cognition (Keefe & Harvey, 2012; Reichenberg, 2010). As previously described, attention is not a unitary construct and can be deconstructed into multiple neuropsychological and/or clinical processes, each with potentially dissociable neurobiological and neuronal substrates. Previous studies investigating attentional impairments in SCZ have applied different theoretical approaches and focused on different facets of the process. Despite such differences in theoretical perspective, this literature can still largely be interpreted in the context of Posner's model of attention, which is currently one of the most accepted models (Posner & Dehaene, 1994). In SCZ, a growing body of evidence suggests impairment in the ability to orient attention towards salient stimuli (Fuller et al., 2006; Luck & Gold, 2008; Mori et al., 1996). The ability to achieve and maintain an alert state was also found to be impaired in SCZ (Dickinson et al., 2007; Fioravanti et al., 2005; Heinrichs & Zakzanis, 1998). Furthermore, the ability to inhibit distraction by goal-irrelevant stimuli when attention is focused on goal-relevant stimuli (i.e., the ability to control attentional focus), was found to be impaired as well (Demeter et al., 2013; Hugdahl et al., 2003; Wahl, 1976). Altogether, these studies point to deficits in the processes of sustained attention in SCZ (Parasuraman & Mouloua, 1987), and this sub-domain is proven to better discern SCZ patients from healthy controls than most other cognitive domains (Nuechterlein et al., 2015). In SCZ, one of the most used tests for assessment of attention is the Continuous Performance Task (CPT) (e.g. Addington & Addington, 1997, Ito et al., 1997, Birkett et al., 2007), which is available in several versions (Kahn et al., 2012). A growing amount of evidence suggests that CPT is able to discriminate SCZ patients from both healthy controls (e.g., Rapisarda et al., 2014, Mussgay & Hertwig, 1990) and non-affected relatives (e.g., Finkelstein et al., 1997; Chen et al., 2004; Wang et al., 2007). During CPT performance, SCZ patients show difficulties in distinguishing target stimuli from non-target stimuli and a reduced perceptual ability to identify a stimulus as a target (Liu et al., 2002). Thus, CPT results potentially suggest that SCZ patients have a specific deficit with sustained attention/impulsivity, rather than attention in general (e.g., Hwang et al., 2015, Liu et al., 1997, Rapisarda et al., 2014). Similar to other cognitive impairments, attentional defects in SCZ are observed not only from disease onset, but also in subjects with high-risk for psychosis (Bora et al., 2014, De Herdt et al., 2013) and during early adolescence in subjects who will develop SCZ (Cornblatt et al., 1999). These impairments persist during symptomatic remissions and, as opposed to other cognitive domains, they are relatively stable across time (Nuechterlein et al., 2014, Wu et al., 2016). Finally, also a percentage of first-degree relatives of SCZ patients exhibit attention impairments (mainly related to processes of sustained attention and alerting/vigilance), supporting their investigation as potential SCZ endophenotypes (Agnew-Blais & Seidman, 2013, Michie et al., 2000).

Although diagnosis of schizophrenia does not depend on presentation of working memory deficits, disruption in working memory is considered an integral feature of the disorder. These deficits can range from impairments in working memory capacity, encoding and semantic organization, impacting positive symptomatology (Arnsten, 2013, Forbes et al., 2009, Goldman-Rakic, 1994, Lee and Park, 2005, Piskulic et al., 2007, Seidman et al., 2003, Silver et al., 2003, Tek et al., 2002), to a failure to retain adequate representation of pleasurable experiences that could motivate future actions, thereby contributing to negative symptomatology (Burbridge and Barch, 2007). Patients with schizophrenia also show impaired spatial planning, as indicated by deficits in spatial serial ordering, planning ability and accuracy (Badcock et al., 2005, Fraser et al., 2004, Hilti et al., 2010). These cognitive deficits are also strongly associated with the negative symptoms of schizophrenia (Kanchanatawan et al., 2017, Yu et al., 2015) and contribute to occupational and social disabilities (Keefe and Harvey, 2012). Working memory deficits in schizophrenia potentially have their origins in

earlier development, as deficits are present not only in chronic patients but also during prodrome in patients with acute psychosis (Frommann et al., 2011). First-degree relatives also often show impaired working memory performance (Conklin et al., 2000). During adolescence, the neural network underlying working memory undergoes significant remodelling, including increased recruitment of fronto-parietal regions, enhanced white-matter structural connectivity between the superior frontal and parietal cortices and greater functional integration of the working memory network, leading to performance gains on tasks of working memory. This process is altered in patients with schizophrenia (Reichenberg, 2010).

As for AD, there is a degree of overlap in the descriptions of attentional and working memory impairments in SCZ. In terms of Posner's model of attention (Posner & Dehaene, 1994), the most severe deficits in SCZ pertain to executive-control and alerting networks, rather than the orienting network (Reichenberg, 2010; van den Heuvel and Fornito, 2014). Functional neuroimaging studies suggest that working memory deficits in schizophrenia are associated with abnormalities in PFC function and reduced connectivity within the working memory network. Particularly, there is reduced connectivity of the fronto-parietal network in the early stage of the disease (Nielsen et al., 2017). Several hypotheses have been suggested regarding the underlying mechanism that leads to these deficits, including impairments in basic perceptual processes within primary sensory brain regions (Lencz et al., 2003), reduced synchronization of pyramidal cells in the PFC due to parvalbumin-positive GABA neuron dysfunction (Gonzalez-Burgos et al., 2015, Hoftman et al., 2017, Lewis et al., 2004), and abnormal anatomical connectivity between prefrontal and posterior brain regions (Sugranyes et al., 2012, Wang et al., 2017, Zhou et al., 2015). In reality, impairments in different cognitive domains interact with each other reciprocally, often resulting in difficulties in separating specific types of dysfunction from other cognitive disturbances (Bachman et al., 2010; Keefe & Harvey, 2012). More work employing the concomitant investigation of different cognitive domains is needed to disentangle the neurobiological basis of different deficits.

Finally, the comparison of cognitive impairments across different neuropsychiatric disorders needs to consider the modulatory effect of several ancillary factors. For example, age (Glisky, 2007), genetics (Greenwood et al., 2014; Stevens et al., 2014) and life history (Kelly et al., 2014a, 2014b) may all interact to confer vulnerability to working memory function or alternatively increase resilience and cognitive reserve (Fabiani, 2012). Furthermore, the presence of comorbid elements, such as depressive (Koppel et al., 2014) or psychotic (Koppel et al., 2014) symptoms, may be associated with greater impairments in both attention and working memory, as well as the exposure to drug regimens with effect on baseline cognitive functions, such as anticholinergic agents (Nishtala et al., 2016).

4. Attention and working memory as determinants of social withdrawal in AD and SCZ

In terms of attribution of causality, it is rare to find social impairments in AD and SCZ described in the context of attention and working memory theories and functions. Social impairments are most typically described as "negative symptoms" of apathy or avolition (Mueser & McGurk, 2004), or may be described as expressions of inappropriate behaviour, e.g. during an episode of psychosis or dense amnesia (Carpenter et al., 1988; Kirkpatrick et al., 2001). Other authors simply account for changes in social function as being caused by changes in personality over the course of illness (Cipriani et al., 2015; Kidd, 2013; Robins Wahlin & Byrne, 2011).

Clearly, higher cognitive functions such as social behaviour are dependent on basic cognitive domains such as attention and working memory. These dependencies are very likely to be reciprocal, where for instance studies of AD patients suggest that social interactions may be potentially protective for cognition, while social isolation may worsen impairment (Bennett et al., 2006; Cacioppo et al., 2016). Interactions are not likely to remain static, such that over time there may be a vicious circle of progressive worsening of cognition and social behaviour that greatly impacts quality of life (Cacioppo & Hawkley, 2009). However, at a more detailed level it is less clear, and not well studied so far, how impairments in attention and working memory may specifically act to disrupt social behaviour and cause social withdrawal. In the broadest sense, interpersonal behaviour can be predicted from profiling of basic cognitive function, utilising tests of processing speed, attention and working memory, together with executive functions and depressive and negative symptoms (Bowie et al., 2008). More specifically, attention deficits can impair social functioning. For example, biases in the processing of social stimuli may be driven in part by attention impairments (Adolphs et al., 2005). In this context, sustained attention may be particularly relevant for the processing of complex social stimuli, such as eye gaze, head and body orientation, facial expression, and pointing gestures (Frischen et al., 2007; Kohler et al., 2000; Tremeau, 2006). Difficulties in sustained attention during infancy are consistently associated with greater social discomfort throughout childhood and adolescence (Perez-Edgar et al., 2010). Attentional deficits may thereby contribute to the aberrant neural representation of social stimuli. Moreover, affective state modulates attention for social stimuli, determining an enhanced response to negative/threatening stimuli when affect is also negative (Cacioppo et al., 2016). This attentional bias may contribute to social impairments both in children (Perez-Edgar et al., 2010) and adults (Bar-Haim et al., 2007; Mogg et al., 2005). In terms of working memory, impairments here are significant predictors of everyday functioning irrespective of the presence of a neuropsychiatric disorder (Giebel et al., 2015). Working memory capacities have been theorised to be a key determinant of processes of self-regulation, an important set of social psychological attributes critical to effective social behaviour (Hofmann et al., 2012). Working memory is a key substrate likely to be involved in aspects of language comprehension, conversational ability and Theory of Mind (Caplan & Waters, 2013; Jones et al., 2016; Laisney et al., 2013), all of which may greatly impact the ability of an individual to engage in social behaviour. Overall, these data point to a link between attention and working memory deficits and social function, but surprisingly few studies have explored this question directly.

Relatively few studies have also directly examined the causal relationships between attention, working memory and social withdrawal in either AD or SCZ. A study of subjects at high-risk of developing SCZ demonstrated that cognitive impairments are capable of modulating social competence and can result in social dysfunction (Jahshan et al., 2012). In a number of neuropsychiatric disorders, including SCZ, autism spectrum disorder and attention deficit hyperactivity disorder, an association is observed between sustained attention impairments and deficits in the processing of emotional valence of faces (Addington & Addington, 1998; Combs & Gouvier, 2004; Tremeau, 2006; Leitner, 2014). Impairments in working memory have been most strongly associated with aspects of negative symptoms in SCZ (Brewer et al., 2006; Cocchi et al., 2009; Pantelis et al., 2004; Pantelis et al., 2009), ranging from psychomotor poverty to outright social withdrawal (Kurtz, 2006). Interestingly, both negative symptoms and working memory impairments in SCZ patients are described to involve the dorsolateral prefrontal cortex, suggesting a partial shared neurobiological background. Thus, while there is some evidence for attention and working memory deficits causing social impairments in AD and SCZ, it is relatively sparse at present. By no means do impairments in attention and working memory provide an explanation for all of the social impairments observed in AD and SCZ patients (e.g., Cusi et al., 2012; Fett et al., 2011).

Attention and working memory impairments have been partly implicated in social withdrawal in AD and SCZ, yet there is no simple cohesive account of underlying mechanisms or a generalised consensus regarding the framework of these relationships. Understanding the potential range of attention and working memory phenotypes across AD

Table 1
Sub-domains of attention investigated by tasks evaluated by the PRISM group. The potential performance characteristics of each assay in terms of the working memory and attention sub-domains described are highlighted.

	Cognitive Subdomains										Reference
Executive-control	Executive-control	Alerting	Orienting	Sustained attention	Other domains	Feasibility/ Robustness	Applicability to patient populations	EEG/fMRI compatible	Reverse Translation	Alignment with previous cohorts*	
Continuous Performance Test-III (CPT-III)	+	+		+	Impulsivity	1	1	1	1 (5C-CPT)	Y (CATIE, GROUP cohorts)	Conners, 2000
Digit Symbol Substitution Test (DSST)	+	+	+		Visual spatial skills	1	1	1	5	Y (CATIE, GROUP cohorts)	Wechsler, 1958°
Choice Reaction Time Test (CRT)		+	+		Motor speed	1	1	1	1 (5CSRTT)	N	Dykiert et al., 2012
Stroop Colour and Word Test (SCWT)	+		+			1	1	2	1	N	Stroop, 1935
Trails Making Test-B (TMT-B)	+				Divided attention	1	1	2	5	N	Brown and Partington, 1942
Digit Span Forward Test (DSF)	+	+		+	Working memory	1	1	3	5	N	Coutinho et al., 2009
Attentional Blink Test (ABT)		+	+		Working memory	1	1	3	5	N	Shapiro et al., 1997
D2 Test of Attention	+		+	+		1	3	3	5	N	Brickenkamp and Zillmer, 1998
Attention Network Test (ANT)	+	+	+			2	1	1	2	N	Fan et al., 2002
Rapid Serial Visual Presentation Test (RSVP)		+			Attentional blink	2	2	1	5	N	Potter, 1976
Paced Auditory Serial Addition Test (PASAT)	+	+		+	Working memory Arithmetic capabilities	2	3	2	5	N	Gronwall, 1977
Posner Cueing Task (PCT)	+		+			2	3	3	3 (e.g. 2 cup digging task)	N	Posner, 1980
Divided Attention Tasks (DAT)					Divided attention	2	3	4	3 (e.g. 2 cup digging task)	N	Moskowitz, 1973
Heindel tasks	+	+	+		Response interference	3	3	4	4	N	Festa et al., 2010
Clock Drawing Test (CDT)	+		+		Working memory	3	3	3	3	N	Luck & Vogel, 1997
Test of Everyday Attention (TEA)	+		+		Working memory	4	3	4	5	N	Robertson et al., 1991

Table 2
List of Working Memory Tasks Considered for Use in PRISM. The characteristics of each assay in terms of the four cognitive subdomains of working memory defined by the CNTRICS initiative are highlighted (Barch et al., 2009a,b). This tables described the working memory and attention tasks evaluation according to the criteria identified by PRISM consortium.

Working Memory Task	Cognitive Subdomains				Feasibility/ Robustness	Applicability to patient populations	EEG/fMRI compatible	Reverse Translation	Alignment with previous cohorts*	Reference
	Goal/active maintainance	Flexible updating	Limited capacity	Interference control						
N-Back Task	+	+	+	+	1	1	1	4 (operant N-back)	Y (NEDSA MD)	Kirchner 1958
Simple Span Task	+		+	+	1	1	1	3	Y (CIBERSAM SZ, PAREL,	Corsi, 1972
Complex Span Task	+	+	+	+	1	2	1	5	NESDO MD, NESDA MD, CATIE SZ)	Redick and Lindsey 2013
Delayed Matching/Non-Matching Task	+		+	+	1	2 (no/few MDD studies?)	1	1 (operant/maze tasks)	N	Squire and Zola-Morgan, 1988
AX-Continuous Performance Task	+	+	+		1	4 (no/few AD studies?)	1	3 (operant or touchscreen 5C-CPT)	Y (CATIE SZ, CIBERSAM SZ, GROUP SZ)	Cohen and Servan-Schreiber, 1992
Spatial Navigation Task	+	+			2	2	3 (few EEG studies)	1 (water maze or other maze tasks)	N	Antonova et al. 2009
Stroop Task Switching	**Executive control : rule generation and selection**				2	3	2	4 (compound discrimination tasks)	N	Cohen et al., 1999
Dot Pattern Expectancy Task	+	+	+		2	4 (no/few AD studies?)	3 (no EEG studies)	4	N	Servan-Schreiber et al., 1996
Letter Number Sequencing Task	+		+	+	2	4 (no/few SZ studies?)	3 (no/few fMRI studies?)	5	N	Redick and Lindsey 2013
Change Detection/ Localization Task	+		+		3	4 (no/few AD studies?)	3 (no/few fMRI studies?)	4	N	Vogel and Machizawa, 2004; Gold et al., 2006
Keep Track Task	+	+	+	+	3	5 (no/few disease studies?)	3 (no/few fMRI studies?)	5	N	Yntema, 1963
Letter/Running Memory Task	+	+	+	+	3	5 (no/few disease studies?)	3 (no/few fMRI studies?)	5	N	Hanlon 1998; Pollack et al., 1959
Self Ordered Pointing Task	+	+	+	+	3	5 (no/few disease studies?)	3 (no/few fMRI studies?)	5	N	Petrides and Milner, 1982
Sequence Encoding and Reproduction Task	+		+		3	5 (no/few disease studies?)	3 (no EEG/few fMRI studies?)	5	N	Dreher et al., 2001
Sternberg Item-Recognition Task	+	+	+	+	3	5 (no/few disease studies?)	2	5	N	Sternberg, 1969
The Ignore-Suppress Task				+	3	5 (no/few disease studies?)	2	5	N	Nee et al., 2007

and SCZ with an aim to potentially subgrouping or reclassifying patients of differing social function will require more extensive and standardized behavioural assessment than is represented in the literature to date. Moreover, as there is no strong *a priori* reason to suspect that any one component of attention or working memory may be of greater relevance than another to deconstruct the complex phenotype of social functioning, it seems reasonable at present for such assessment to interrogate as broad a range of sub-domains of both processes as possible.

5. Factors influencing tasks used for behavioural phenotyping

The list of potential attentional and working memory tasks that could be included in a deep behavioural phenotyping exercise is extensive. Many tasks have been developed to disentangle and measure sub-components of attention and working memory under different investigational settings, and some of these have been reviewed in extensive detail previously (Nuechterlein et al., 2009; Barch et al., 2009a).

The first exercise completed by the PRISM attention and working memory groups was to review how well a variety of commonly used tasks that the groups had experience of using were capable of measuring differing sub-components of each process. The goal was to make sure that all sub-components of attention and working memory were capable of being assessed by at least one test in the battery (Tables 1 & 2). Secondly, as the vast majority of cognitive tests have been adopted from the disciplines of experimental psychology and neuropsychology, they often suffer from a number of limitations that can make them suboptimal in clinical trial settings. With this in mind, the PRISM project decided on the following set of criteria to guide the choice of tasks for the phenotypic battery (Kas et al., 2018; van der Wee et al., 2018; Bilderbeck et al., 2018, this issue):

5.1. Feasibility and robustness of implementation

Clinical trial environments are inevitably constrained by financial and temporal resource; assay selection must consider these factors. Tasks which require less training to administer reduce chances of experimental error (Kozora et al., 2007). Tasks must also be sufficiently harmonized in their administration between laboratories that they will robustly assess individual differences (Costa et al., 2017)

5.2. Applicability to the patient populations

Given the nature of the patient populations under study, patient burden is a significant concern. At the most basic level, patients must be able to understand and complete the tests administered. Tests with complex instruction or lengthy administration time may negatively affect compliance rates (Meyers & Brown, 2006). An absence of task practice effect is desirable as it improves the ability to detect changes in cognition (Bartels et al., 2010; Beglinger et al., 2005; Pietrzak et al., 2010), and rules out a potential confound between differing patient populations. Tests should possess good psychometric properties for the patient populations in question (no range restrictions, normal distribution of data and high reliability), which may improve sensitivity for detection of subtle changes in cognition (Collie et al., 2007).

5.3. Compatibility with EEG and fMRI analyses

Not all tests are paced adequately or generate appropriate events to which neurophysiological signals can easily be related. This is an important consideration if a deeper understanding of the neurobiological substrates at play is to be discerned.

5.4. Potential for reverse translation

The greatest ability to interrogate the neurobiological and neuronal substrates of the processes in question is given by the ability to test these systems equivalently in animal models.

5.5. Alignment with instruments used in previous patient cohorts

The PRISM project aims to utilise existing patient cohort datasets that have been made available to bolster the evidence generated by the ongoing clinical trial. It will confer advantage if at least some of the chosen tasks bear some relationship to previously implemented protocols.

Tables 1 and 2 summarise the value judgements made by the group for each of the above criteria for the attention and working memory assays, respectively. Ultimately, the choice of assays to assess two domains of function in a complex patient cohort will inevitably involve careful consideration of a number of compromises related to operational pragmatism. In addition, the review process clearly highlighted, maybe unsurprisingly, that there has been a lack of systematic approach or uniformity to the study of attention and working memory across clinical populations such as AD and SCZ patients to date.

6. Selected Methodologies

From the shortlists highlighted in Tables 1 and 2, the final tasks to be used for the PRISM clinical trial were selected. In this section, a detailed discussion is provided of the pros and cons of the tasks the PRISM expert groups identified as most likely to satisfy the requirements of the project. The chosen attention assay methodologies were the Continuous Performance Test-III, Attention Network Test, and the Digit Symbol Substitution Test, and for working memory were N-Back, complex span and “Spatial Navigation/Virtual Environment” (SN/VE) tasks (Table 3). The exact details of each task as they will be employed in the PRISM phenotypic battery are described elsewhere in this issue (Bilderbeck et al., 2018, this issue).

6.1. Attention Tasks

6.1.1. The Continuous Performance Test III (CPT-III)

The Continuous Performance Test III (CPT-III) is an attention task that is widely used in clinical research to measure inattentiveness, impulsivity, vigilance, and sustained attention (Fig. 1). It is particularly well suited for the study of executive-control subcomponents of attention. CPT-III demonstrates excellent internal consistency, good validity, and high test-retest reliability (Conners et al., 2000). CPT-III is a task-oriented computerized assessment in which subjects are instructed to press the space bar on a standard keyboard whenever they are presented with any letter, except “X”. The typical test length is 14 minutes, comprising 360 trials. Measures collected include correct detection (number of times the subject responded to the target stimulus); omission error (number of times the target was presented, but the subject did not respond); commission error (number of times the subject responded when no target was presented); reaction time (the amount of time between the presentation of the stimulus and the subject's response). These parameters can be combined to provide a global measure of attention. The task has been repeatedly utilized in AD, SCZ and major depressive disorder (MDD) patients to measure attentional deficits as well as effects of pharmacological interventions (Chau et al., 2017; Harmell et al., 2014; Lee et al., 2016; Lysaker et al., 2010; White & Levin, 1999). Normative data is readily available, allowing control for age and educational level. The CPT-III task has been previously used in both SCZ (including the CATIE cohort and CNTRICS) and AD populations, where deficits are robustly observed (e.g. Hwang et al., 2015; Liu et al., 1997; Rapisarda et al., 2014).

Literature data suggests that SCZ patients may show CPT-III deficits

Table 3
The Shortlist of Selected Attention and Working Memory Test Modalities. This tables highlights the attention and working memory test modalities that were nominated for use in PRISM. Value judgements of the relative merits (pros & cons) of each assay as determined by the working groups are included, as well as some highlighted details of the exact test variant used in the PRISM trial.

	Task Selected	Pros	Cons
Attention	**CPT-III**	1. Robust & validated 2. Easy to implement 3. Allows EEG/fMRI integration 4. Simple back translation 5. Normative data for age and SCZ	1. Medium time of administration (20 min) 2. Age sensitivity 3. Drug sensitivity
	ANT	1. Robust assessment of executive control 2. Favourable psychometric properties 3. Test-retest reliability 4. Short test time (~15-20 min) 5. Freely available online versions 6. Good EEG/fMRI literature 7. Molecular genetic studies available	1. Confounds relating to orienting behaviours 2. Back translation not available
	DSST	1. Robust & validated 2. Easy to implement 3. Short test time (< 5 min) 4. Allows EEG integration 5. Home test possible	1. Practice effects 2. Difficult (f)MRI integration 3. Intense motor/working memory components 4. Back translation not available 5. Age sensitivity 6. Drug sensitivity
Working Memory	**N-Back**	1. Robust & validated 2. Easy to implement 3. Many test variants 4. Home test possible 5. Short test time (< 15 min) 6. Allows EEG integration 7. Extensive fMRI literature 8. Normative data for age	1. Parametric sensitivity 2. Difficult back translation
	Spatial Navigation	1. Easy to implement 2. Simple back translation 3. Short test time (< 15 min) 4. Good fMRI literature 5. Assessment of spatial WM	1. Weaker clinical validation 2. Limited EEG work 3. No normative data
	Complex Span	1. Robust & validated 2. Easy to implement 3. Many test variants 4. Home test possible 5. Short test time (< 15 min) 6. Normative data for adults	1. Difficult back translation 2. Relatively difficult EEG/fMRI integration

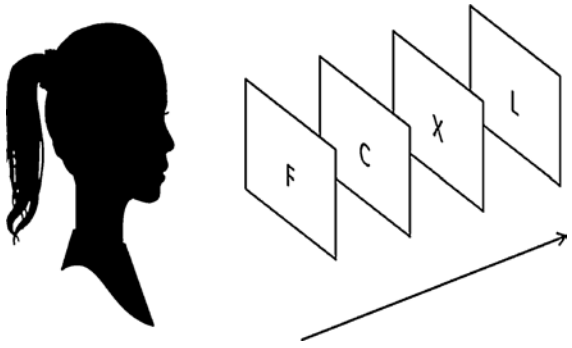

Fig. 1. Basic Operation of the Conners Continuous Performance Test - III. A series of individual letters are presented on a screen. Subjects must press a key each time a letter appears unless it is an "X", to which they must withhold responding.

more closely associated to impulsive decision-making behaviors (fast reaction time, high commission error rate, low response criterion thresholds) (e.g., Liu et al., 2002), whilst the impairments in AD may be associated with difficulties in sustained attention (e.g., Berardi et al., 2005; Mendez et al., 1997). Interestingly, in SCZ patients, poor performance correlates with low self-esteem, anxiety and rumination, all features that suggest an internal distraction from externally generated signals (Lysaker et al., 2009). CPT-III performance has been shown to activate an extensive network covering frontal, parietal and occipital areas (Bartes-Serrallonga et al., 2014). It further permits EEG integration and has demonstrated favourable translational properties (Young et al., 2013), including an fMRI-compatible version of the task (McKenna et al., 2013) in which activation of the fronto-striatal and parietal structures was noted.

6.1.2. The Digit Symbol Substitution Test (DSST)

The Digit Symbol Substitution Test (DSST) is a subtest of the intelligence test introduced by Wechsler (Wechsler, 1958). It requires participants to replace a series of digits by geometric symbols relative to a digit-symbol key provided in a limited amount of time (Fig. 2). The test is very quick (90 seconds) and can be easily implemented in most experimental settings. As DSST is sensitive to various cognitive processes including processing speed, sustained attention, visual spatial skills, set shifting, and working memory, it is perhaps better viewed as a more general measure of cognition, as compared with contemporary tasks that parse more specific aspects of attention (Amaresha et al., 2014). Nevertheless, its value has been clearly demonstrated through its repeated application in various neuropsychiatric populations, with solid evidence of impaired performance in AD and SCZ, and treatment effects in MDD (Frampton, 2016; Grootens et al., 2009; Gurnani & Gavett, 2017; McIntyre et al., 2014). It permits greater discrimination of SCZ patients from healthy controls than the more widely studied neuropsychological instruments (Dickinson et al., 2007), and a variation of the DSST was included in the MATRICS consensus battery for SCZ (Nuechterlein et al., 2008). Poorer DSST performance has been associated with disability (Brekke et al., 2007) and other symptoms in SCZ patients, such as affective flattening and alogia (Amaresha et al., 2014). In AD, it has been extensively used as a measure of general

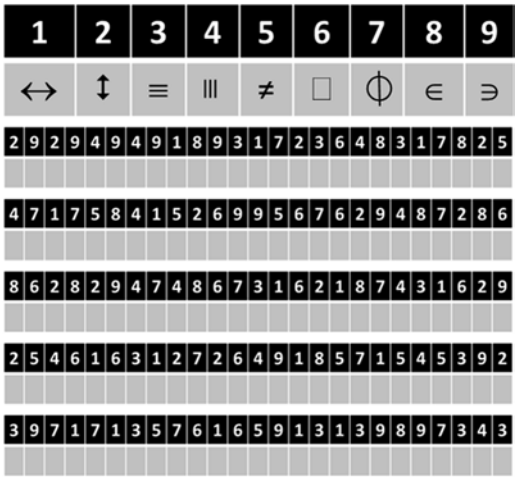

Fig. 2. Basic Operation of the Digit Symbol Substitution Test (DSST). DSST provides subjects with a key of nine digit-symbol pairs, followed by a list of digits to which they must respond. Under each digit, subjects must write the corresponding symbol as fast as possible within a limited amount of time. The number of correct symbols is measured.

cognitive function and as an outcome measure for treatment response (Connelly et al., 2005). DSST demonstrates a good validity and reliability. Finally, the DSST has been used in previous patient cohorts available to PRISM, such as CATIE and GROUP cohorts. One point of awareness is that use of assays involving more complex visual symbols or digits needs to consider the cultural context in which the test may be conducted, as these symbols or digits may not have the same salience in different regions.

Several versions of DSST allow integration with different neurophysiological platforms. For example, a parametric version has been developed that minimizes decisional and motor requirements, thereby providing more reliable assessment of memory components (Bachman et al., 2010). In fMRI studies, the DSST is often presented as individual digit-symbol pairs, where the subject has to press to make an accuracy decision relative to the provided digit-symbol key. This imaging friendly task variant is sometimes called a 'yes/no' digit-symbol substitution test or symbol-symbol substitution test. DSST has also been combined with EEG (Greenblatt et al., 2005) and near-infrared spectroscopy (Nakahachi et al., 2008). These DSST variants activate frontoparietal networks known to be associated with working memory, where the intensity of activation is found to scale with task reaction time (Rypma et al., 2006).

6.1.3. The attention network test (ANT)

The attention network test (ANT) (Fan et al., 2002) has substantially improved our knowledge of attentional processing due to its ability to independently quantify multiple subcomponents of attention. ANT captures 12 distinct conditions measuring various aspects of attention including alerting, orienting and executive control (Fig. 3). Subjects are presented with a center target arrow, pointing either left or right, and are required to indicate its direction. The target arrow can be flanked either by neutral (horizontal bars), congruent (pointing in the same direction as the target) or incongruent (pointing in the opposite direction to the target) arrows, but the subject must respond only to the direction of the central target arrow. The target arrow can also be preceded by different warning cues: no cue, central cue (central fixation point), double cue (above and below the central fixation), and spatial cue (above or below, indicating the location of the subsequent target). All cues and flanker types are equiprobable and presented randomly. Subjects are required to respond to the central target as quickly and as accurately as possible. ANT is a relatively quick (~25 minutes) and simple computerized task, but arguably may be a little too long to be ideal in a broad phenotypic battery, potentially raising patient burden and compliance issues. ANT has demonstrated good validity with acceptable reliability (Fan et al., 2002; Macleod et al., 2010) and, since its introduction, it has been applied in numerous neurological and psychiatric population studies (more than 70 independent studies are reported on MEDLINE) including AD, SCZ and MDD (Epstein & Kumra, 2014; Fuentes et al., 2010; Orellana et al., 2012; Tian et al., 2016).

ANT was deliberately established as a test to probe different attention networks, and has been used in conjunction with fMRI (e.g. Markett et al., 2014) and EEG (Missonnier et al., 2013) methodologies. Theoretically, ANT should separately activate these brain networks thus permitting the detection of specific and global attention impairments (for detail see Fan et al., 2002). The different attentional components measured by ANT have been linked to the activation of thalamic, anterior and posterior cortical and anterior cingulate regions (Fan et al., 2005). Some studies have also used the ANT test to assess the relationships between networks during attentional performance (Macleod et al., 2010).

6.2. Working Memory Tasks

6.2.1. N-Back Tasks

N-back tasks (Kirchner, 1958) remain some of the most commonly used tests of working memory in the cognitive neuroscience field. They are a well-validated and a widely-used means of manipulating working memory capacity and its response requirements. In the broadest sense, n-back is a form of continuous performance testing where subjects are presented with a sequence of stimuli and have to decide when the current stimulus is correct based on an "n-back" rule, i.e. whether the current stimuli matches that presented n steps back in the sequence (Fig. 4). Previous task variants have used a number of different stimulus sets, including letters, words, emotional words, numbers, faces, shapes, odors, pictures, auditory tones and fractals (Owen et al., 2005). Although performance on n-back tasks relies on multiple psychological processes, performance is largely independent of the stimuli and materials used. The critical independent variable of a basic n-back task is the load factor *n*. By varying *n*, working memory capacity and relative difficulty of task performance can be systematically manipulated. Task performance is typically measured through the dependent variables of accuracy and reaction time. Task difficulty and the strategy by which subjects complete the n-back task can also be influenced by the introduction of "lure" stimuli. Lures are stimuli that would be correct in position *n*, but occur at positions *n-1* or *n+1* in the sequence (Kane et al., 2007). Lure stimuli act as false alarm signals that require more inhibitory control and cause more interference with ongoing processing than other less salient, non-lure stimuli (Gray et al., 2003; McCabe & Hartman, 2008; Oberauer, 2005). Another means of more strongly taxing active maintenance and interference control processes is offered via dual n-back tasks (Jaeggi et al., 2010), where subjects have to simultaneously perform two n-back tasks with different stimulus sets. With these variants, n-back tasks are thought to efficiently measure all working memory sub-domains (Barch et al., 2009a) (Table 2).

N-back tasks have favorable characteristics for integration with other measures of brain activity. From a functional imaging perspective, performance on N-back tasks has been shown to activate areas of frontal and parietal cortex including medial and lateral premotor cortex, cingulate cortex, dorsolateral and ventrolateral prefrontal cortex, and medial and lateral posterior parietal cortex, in healthy volunteers (Barch et al., 2013; Owen et al., 2005) as well as in clinical populations (Harvey et al., 2005). Nonetheless, some differences in the pattern of activation exist between healthy controls and both SCZ (Bleich-Cohen et al., 2014; Jansma et al., 2004; Koike et al., 2016; Schneider et al., 2007) and AD (McGeown et al., 2008; Yetkin et al., 2006) patients, probably suggesting a compensatory process to counterbalance decreased working memory capacity. Evidence suggests that brain activations associated with N-back performance are reliable

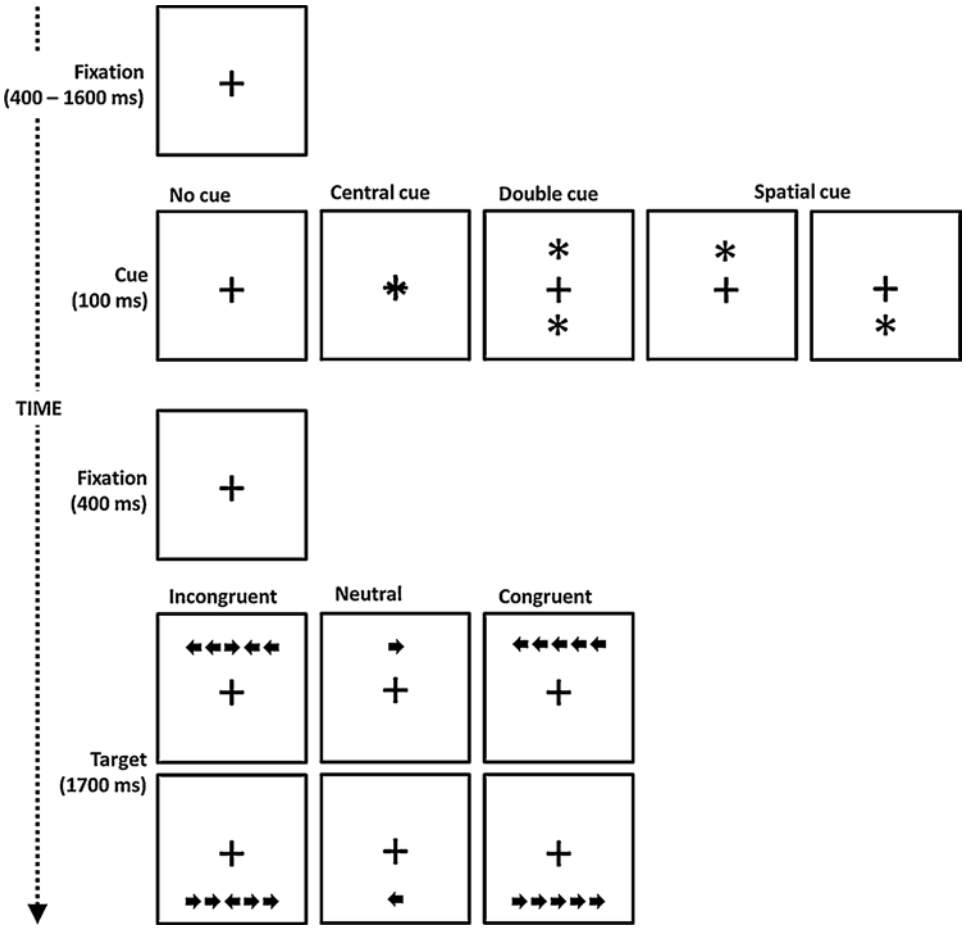

Fig. 3. Basic Operation of the Attention Network Test (ANT). A typical ANT procedure is illustrated. Subjects are presented with target arrows on a screen, and are required to indicate the direction they are pointing. Target arrows can be preceded by a cue, and can also be flanked by congruent and incongruent arrows. All cues and flanker types are equiprobable and presented randomly.

across subjects (Drobyshevsky et al., 2006) and time (Caceres et al., 2009).

As input and output aspects of the N-back (i.e. the nature of the stimuli and the response requirements) do not vary with increasing working memory load, this is a major advantage for electrophysiological studies. In healthy subjects, increased working memory load will decrease EEG parietal alpha and beta frequency band power, increase frontal theta power and decrease P300 amplitude (Chen et al., 2008; Gevins et al., 1997; Gevins & Smith, 2000; Watter et al., 2001). In SCZ patients, excessive frontal gamma oscillatory activity and reduced frontal beta activity have been demonstrated during N-back testing (Barr et al., 2010). To the best knowledge of the authors, there have been no EEG studies of N-back performance in AD patients to date.

6.2.2. Complex Span Tasks

In simple span tasks, subjects are presented with a list of items to recall that increase in size until accurate recall fails. However, simple span tasks are not considered to adequately capture aspects of working memory related to the active manipulation of temporarily stored items, and often bear little correlation with performance in other working memory tasks (Daneman, 1980). While backwards span tasks have been described and address this issue to a degree (Smyth & Pelky, 1992), complex span tasks (Fig. 5) were developed to offer more opportunity to measure working memory processes reliant on both the storage and processing of information (Unsworth, 2009), the results of which are more suitable for broad phenotypic profiling. Complex span tasks efficiently test all four working memory-subdomains, whereas in

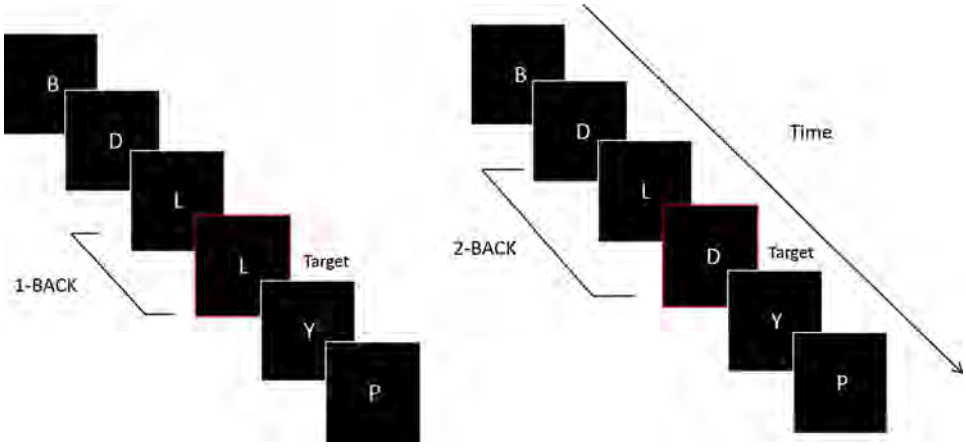

Fig. 4. Basic Operation of the N-Back Test. The N-back test is a continuous performance test where subjects have to attend to a sequence of briefly presented stimuli (in the case of this example, letters) and indicate a correct response when a stimuli that is presented matches that presented n-trials previously. Left: the second presentation of the letter "L" is correct in this 1-back example, as "L" was just presented one trial previously. Right: in this 2-back example, the second presentation of the letter "D" is correct.

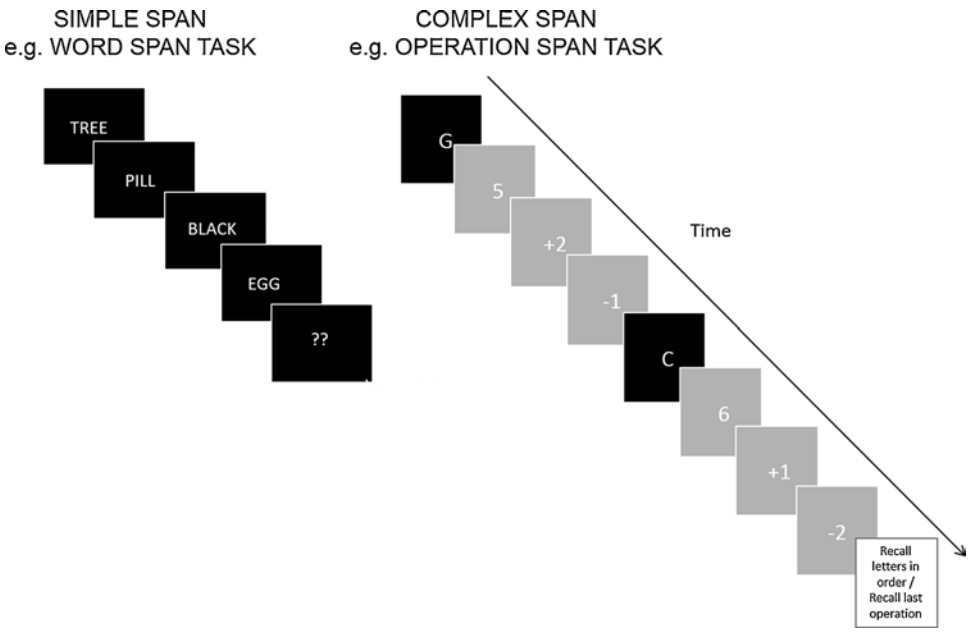

Fig. 5. Basic Operation of the Span Test. Examples of a simple span task (word span, left) and complex span task (operation span, right). The word span task consists of serial presentation of a list of to-be-recalled stimuli. The stimuli are presented individually, typically one per second, and at the end of a series, the subject is required to recall the list in correct serial order. Complex span tasks employ the use of a simple span stimulus list to be recalled, but also require an additional task to be performed in-between simple span recalls. Subjects thereby must not only memorize items, but must perform an additional cognitive manipulation. The example presented on the right is a sample from an operation span task involving two operations and a two-letter load. Subjects are asked to recall all the letters presented and also recall the last operation in the sequence. In this case, the first operation is "5 + 2 − 1 = 6" and the second operation is "6 + 1 − 2 = 5", therefore the correct response is "GC5".

comparison simple span tasks have a poorer ability to test "flexible updating". Complex span tasks involve the alternating presentation of a processing task (e.g. comprehension or arithmetic) with a simple span memory storage task. The first complex span task to be described and incorporated into practice was the reading span task (Daneman, 1980). In this task, following a period of practice subjects read sentences and judge their comprehension while alternately trying to remember an increasing list of unrelated letters. In the most common task variant each sentence contains 10-15 words, of which half presented during the test are incomprehensible. After making a judgement on sentence comprehension, subjects are then briefly presented with a letter which forms part of an increasing list to be recalled in sequence. List lengths can vary from three to seven, and typically three trials are given for each set-size. A common non-verbal variant of the complex span task is the symmetry span task (Barch et al., 2009a). With this test, processing load is tested as subjects view matrices of red squares and have to make judgements regarding their vertical symmetry. Memory capacity is tested with the alternating presentation of a matrix of squares that increases in size, where subjects have to recall the sequence in which squares were added to the matrix. Automated versions of the reading and symmetry span tasks have been described (Unsworth, 2009), as have several other variants utilising a variety of different stimuli (e.g. listening and operation span tasks). For complex span tasks, the independent variable of the processing sub-task is task difficulty, while for memory capacity it is list length and saliency. Accuracy and response latency measures can be measured as dependent variables for each sub-task. A partial storage score can also be used for the memory capacity sub-task, which is the sum of items recalled in the correct serial position regardless of whether the entire trial was recalled correctly (Redick & Lindsey, 2013). Previously published studies have reported relatively small practice effects and high test-retest reliabilities for reading span (0.82) and symmetry span (0.77) tasks (Redick & Lindsey, 2013). Some studies suggest that the correlations among different complex span tasks are only modest (e.g. Redick & Lindsey, 2013), suggesting that the different paradigms applied may test partially different neurobiological substrates (e.g., Colom et al., 2006; Unsworth et al., 2009). Not all studies are in agreement with this finding, however, and once measurement error and paradigm specific sources of variance are excluded, some high correlations have been reported between span tasks and other tasks of memory (Wilhelm et al., 2013; Schmiedek et al., 2014). Nonetheless, other pragmatic factors related to patient populations under assessment could influence the exact choice of complex span paradigm used, such as visual, verbal or auditory capacity.

While relatively few neuroimaging studies using different complex span tasks, contrasts and response requirements (e.g. recall, cued recall, recognition) have been conducted, they potentially suggest a common recruitment of lateral prefrontal cortex, anterior cingulate and posterior parietal cingulate areas during task performance (Bunge et al., 2000; Chein et al., 2011; Kondo et al., 2004; Osaka & Osaka, 2002; Osaka et al., 2004; Smith et al., 2001). These regions are nodes in a fronto-parietal network that is commonly associated with working memory processes (Funahashi, 2017). Other regions can be recruited by other tasks, for instance, by use of an operation span task to reveal hippocampal engagement and its functional specialization during working memory encoding (Faraco et al., 2011).

Complex span tasks have not been extensively studied in combination with electrophysiological methods. Only one study has recently compared the within-subject EEG profile associated with N-back, simple digit span and complex operation span task performance (Scharinger et al., 2017). Globally, decreases in alpha and beta ERD, theta ERS and mean P300 amplitude were observed during performance of all three tests. Nonetheless, the profiles were somewhat discrepant to theoretical accounts of working memory processes taxed by each test, making interpretation of the functional meaning of the EEG profiles less straightforward (Scharinger et al., 2017).

6.2.3. *Spatial Navigation/Virtual Environment (SN/VE) Tasks*

While often overlooked, working memory processes across several domains are involved in both environmental learning, orientation and spatial navigation abilities (Baumann et al., 2011; Gras et al., 2012; Meneghetti et al., 2016; Weisberg & Newcombe, 2016). There are several ways that spatial navigation has been tested in humans, from real world navigation tasks (e.g. Brunye et al., 2015; Claessen et al., 2016; Laczo et al., 2017), including walking versions of the Corsi Block test (Bianchini et al., 2014; Palmiero & Piccardi, 2017; Piccardi et al., 2008; Piccardi et al., 2013; Piccardi et al., 2015) to other laboratory-based span and maze tests (Ayaz et al., 2011; Bertholet et al., 2015;

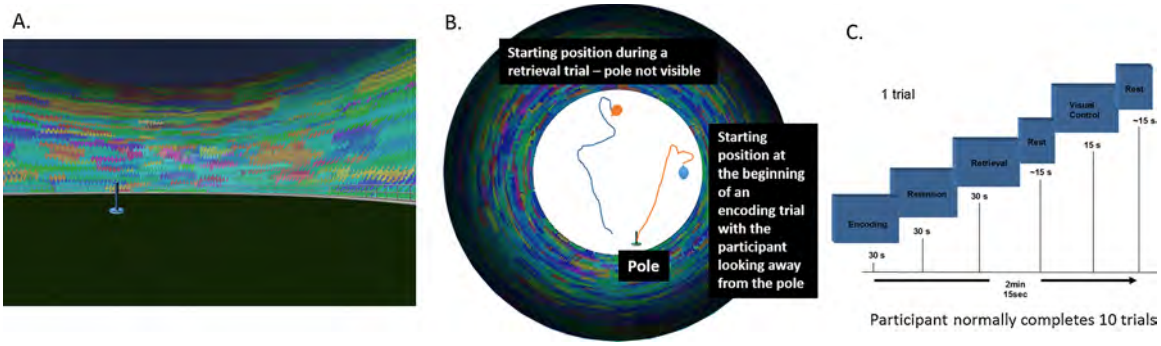

Fig. 6. Basic Operation of the Spatial Navigation in Virtual Environment Task. SNVE tasks are conducted in virtual environments resembling a sports arena. A. The virtual environment in this case is a circular stadium with spectators in the seating areas wearing different team colour clothes to create abstract patterns which can serve as allocentric cues. B. A flag or pole in the playing area serves as the target location to navigate towards. C. During encoding trials, the subject learns to navigate towards the pole using a joystick, and then during the retrieval trial the pole is removed and the subject has to navigate to where they think the pole should be. In the allocentric test variant, the retrieval test session start position is varied and the subject must use the allocentric wall cues to find the goal location. In the egocentric test variant, the subjects start from the same location during retrieval trials as during encoding trials, however the wall patterns are rotated to prevent them from indicating the goal location. Instead, subjects must use egocentric cues and move relative to their own body axis to find the goal location.

Della Sala et al., 1999; Kessels et al., 2000; Krieger et al., 2001; Millet et al., 2009; Mitolo et al., 2017; O 'Connor & Glassman, 1993; Pickering et al., 2001). More recently, there has been a rise in use of navigational tasks utilizing computer generated virtual environments (Fig. 6). Generally, in these tasks, subjects are required to navigate a virtual environment (e.g. a stadium or outdoor location) towards a marker destination (e.g. flag) during encoding trials, and must then re-navigate to those now unmarked locations in retrieval trials. Virtual spatial navigation tasks can be used to assess spatial learning and memory abilities and deficits in healthy, aged and diseased subjects with relatively less burden than a real world setting might have. To specifically tax spatial working memory, spatial navigation tasks have to be designed in a way that necessitates the maintainance and manipulation of spatial information to guide a correct resonse (for instance, by incorporating a delayed recall or span element to the problem solving). These tasks are thought to test mainly the the goal/active maintenance and flexible updating working memory subdomains (Table 2). Topographical disorientation and disturbances of egocentric topographical working memory are well described problems in AD (Bird et al., 2010; Mokrisova et al., 2016; Morganti et al., 2013; Pai & Jacobs, 2004; Serino et al., 2014) and MCI (Antonova et al., 2009; Laczo et al., 2010), as well as in SCZ (Fajnerova et al., 2014; Ledoux et al., 2014; Salgado-Pineda et al., 2016). It has been posited that spatial memory deficits are the best indicator for poor social and occupational functioning in SCZ (Green, 1996; Green & Nuechterlein, 1999), pointing to the relevance of spatial memory tasks to socio-cognitive symptoms.

SN/VE Tasks reliably activate hippocampal and mediotemporal brain regions under fMRI (Parslow et al., 2004). The ability of elderly participants to navigate to previously learned spatial locations was found to be impaired compared to the young group and correlates with their attenuated hippocampal activation (Antonova et al., 2009). Finally, a pharmacological study in healthy subjects suggests a reliance on distinct cue/landmark learning rather than place or spatial learning where hippocampus functioning is altered (Antonova et al., 2011).

6.3. *Reverse translation of human tasks*

Animal models form a crucial component in the ability to dissect neuronal circuits responsible for cognitive processing and social function (e.g. Russell, 2011; Yan et al., 2009). Animal models permit us to record and perturb functional neuronal circuits at multiple spatiotemporal scales and with unprecedented specificity (e.g. Knopfel, 2012; Kramer et al., 2013; Wulff & Arenkiel, 2012; Yan et al., 2010). However, there are a number of issues that can limit back translation of human cognitive tasks, including tasks of attention and working memory. A major problem comes from definition of the processes themselves, at least in the case of working memory. Animal researchers have historically used the term working memory in a slightly different sense to human researchers, where typically its usage relates to short-term or trial unique aspects of a process with much less emphasis on the concept of manipulation of the representation (Puig et al., 2014; Tsutsui et al., 2016). This is somewhat due to difficulties in establishing tasks that unequivocally measure the ability of a rodent to manipulate a representation in working memory (Dudchenko et al., 2013), although there have been some interesting attempts to do so (Pontecorvo et al., 1996). It should also be acknowledged that there may simply be no exact homologues of some human working memory processes in rodents (Dere et al., 2017; Premack, 2007). Moreover, rodents exhibit a much more limited working memory capacity in standard tests in comparison to humans (Horner et al., 2013; Matzel & Kolata, 2010), although somewhat improved results can be obtained in more naturalistic settings (Oomen et al., 2013; Vorhees & Williams, 2014a, 2014b). There are also major differences in the ability to assess behaviour related to rule-switching, where a rule switch that a primate can acquire in less than a single session (Moore et al., 2005; Stoet & Snyder, 2009) can require weeks of training in rodents (Brigman et al., 2005; Hvoslef-Eide et al., 2016). Training times are particularly relevant in this context, as they can quickly become incompatible with a number of the more aggressive AD transgenic disease models, where pathology and function can markedly decline over a period of few months (Blackmore et al., 2017; Jul et al., 2016; Przybyla et al., 2016; Xu et al., 2014). Finally, while human cognitive tasks are predominantly visual, rodents naturally acquire olfactory, somatosensory and auditory tasks relatively more rapidly (Frederick et al., 2017; Horner et al., 2013; Jaramillo & Zador, 2014; O'Connor et al., 2013; Poort et al., 2015). Taking into account these limitations, the following preclinical tasks were suggested as the most appropriate preclinical homologues of the nominated human assays.

6.3.1. *Attention test homologues*

CPT-III. Tasks targeting sustained attention have been widely established for use in rodents. One such example is the **five-choice**

continuous performance task (5C-CPT) (Cope & Young, 2017). The 5C-CPT, is a continuous-performance paradigm that is easily implemented in most types of operant-conditioning box (Young et al., 2009), and it has been widely used both in the context of clinical (e.g. Koike et al., 2016; Reverte et al., 2016) and basic research (e.g. Guillem et al., 2011; Kim et al., 2016). Other variations on continuous-performance paradigms and continuous change-detection tasks have also been applied successfully in rodents (Gritton et al., 2016; Hvoslef-Eide et al., 2016; Kim et al., 2015; Zhang et al., 2014). Combining such tasks with optogenetic techniques for recording and perturbing neuronal interactions, recent studies have helped to identify the neuronal pathways that may form the basis of attentive behavior (e.g. Guillem et al., 2011; Kim et al., 2016; Zhang et al., 2014).

ANT. While an exact homologue of the ANT is not available, a range of attention tasks could be used to examine all three components of the ANT investigational model. For example, in terms of assessing the executive-control network, **attentional set shifting tasks** probe the ability to resolve conflict between competing sources of information. The most widely version of the task in rodents so far has been the 2-cup digging paradigm. (Birrell & Brown, 2000; Brown & Tait, 2016; Colacicco et al., 2002; Garner et al., 2006). Here, animals dig for food reward in one of two cups, where the correct decision depends on two different sensory dimensions (typically odor versus digging medium). Animals are then progressed through a series of differing contingencies (discrimination, reversal, intradimensional and extradimensionsal set shifting) which tax processes of executive-control. Other touchscreen-based paradigms have back-translated set shifting tasks more directly by presenting visual stimuli that can be classified along two different visual dimensions (Bissonette & Powell, 2012; Brigman et al., 2005). Finally, recent studies in head-fixed mice have used cross-modal task switching – either between visual and auditory (Wimmer et al., 2015) or visual and olfactory cues (Poort et al., 2015). Compared to the touchscreen-based approach, both the 2-cup digging task and cross-modal switching tasks seem to work as better assays of attentional set shifting because of shorter training times and lower cognitive loads (Poort et al., 2015). In terms of the orienting network, **distractor/flanker tasks** can be used in rodents to examine their ability to orient towards relevant sensory information. A number of tasks have also employed sensory distractors or flanker stimuli in rodents (Meier et al., 2011; Newman & McGaughy, 2008; Newman et al., 2015). These tasks are easily applied in rodents because cognitive load is increased through the number of items per trial, rather than exerting additional (and confounding) demand on working memory, behavioral flexibility or extensive rule learning. Finally, sustained attention tasks (such as 5C-CPT) measure the ability to obtain and maintain alertness. Used together, these tasks could effectively provide data homologous to the human ANT, although this would incur a significant resource burden.

DSST. The five-choice serial-reaction time task (5CSRTT) has been proposed as a possible animal homologue of DSST, but the constructs measured by these two tasks are not likely to be similar. Given the level of symbol comprehension required for human task completion, it is difficult to envisage that there could be a close homologue of this test in rodents.

6.3.2. Working memory test homologues

6.3.2.1. N-back. There have been relatively few attempts to determine a homologue in rodents, although an operant box n-back procedure has been described (Ko & Evenden, 2009). However, it remains to be demonstrated that this homologue is really interrogating the same psychological process as the human n-back tasks assess. Using a discrete trials approach, rats are presented with series of lever extensions in a 5-choice chamber to generate stimulus "lists" to be remembered. A recall challenge is presented at the end of each sequence where all levers are presented, and the correct choice is given by the pressing the lever at position *n* in the list. Using this task, rats could readily perform a 1-back condition, but required substantial training to reach criterion 2-back performance. Rats were unable to learn a 3-back condition. This data raises the question of whether > 2-back performance is a real biological limit for rats or simply represents a training/procedural artifact. Due to limited work conducted with this task, and little other alternative n-back approaches described for rodents, this remains somewhat of an open question. While delayed matching and nonmatching procedures in rodents (e.g. Dunnett, 1985; Robinson & Mao, 1997; Rogers et al., 1992) arguably represent the closest homologue to a human n-back task in routine use, and temporal relational memory tasks have also been described (Dudchenko, 2004), the psychological discrepancies of task performance between species may well be significant.

6.3.2.2. Span tasks. Olfactory and spatial versions of simple span tasks have successfully been employed in rodent studies. In odor span tasks, rats learn to dig in differently scented bowls of sand for food reward (Dudchenko et al., 2000; Dudchenko, 2004; Young et al., 2007). For each successfully completed trial, another differently scented bowl is added to the arena. Correct performance is determined by a non-matching to sample rule, i.e. the most recent/novel scented bowl contains the food reward. Memory span is measured by the number of odors the animal can remember before it makes a mistake. The measure of memory span in this task is sensitive to pharmacological manipulation, where ketamine, NMDA antagonists, AMPA antagonists and scopolamine decreased working memory span (Davies et al., 2013; Galizio et al., 2013; MacQueen et al., 2011; Rushforth et al., 2010; Rushforth et al., 2011), whereas nicotine increased span (Rushforth et al., 2010; Rushforth et al., 2011). In spatial span task variants, rats are trained to remember the locations of previously visited bowl (Dudchenko et al., 2000) or goalbox (Steele and Rawlins, 1989) rather than its odor. Span tasks have also been successfully employed in mice and monkeys (Murray & Mishkin, 1998; Young et al., 2007). Tg2576 mice (transgenically over-expressing human amyloid precursor) have shown age-dependent deficits in the odor span task (Young et al., 2009), demonstrating the potential of this task in combination with rodent disease models. Although theoretically possible to repeatedly expose animals to span tests for assessment of the efficacy of different drugs, it remains a low-throughput approach with a long, manual training component that somewhat limits utility for discovery research. There are no reports of any methodologies to test rodents with complex span protocols.

6.3.2.3. Spatial Navigation/Virtual Environment tasks. Spatial working memory (as defined by preclinical behaviourists at least), is a cognitive domain that is readily accessible for measurement in rodents and has been fairly well studied. Of the three working memory assay types nominated, spatial navigation probably offers the most options when it comes to reverse translation. One of the canonical paradigms here is the water maze (Morris, 1981), a standard paradigm for the testing of spatial navigation in rats and mice. The water maze test is highly sensitive to hippocampal lesions in rodents, and also in humans (Parslow et al., 2004). Beyond the water maze, many different types of mazes and environments have been used to test spatial navigation (Dere et al., 2017; Hodges, 1996; Tsutsui et al., 2016; Vorhees & Williams, 2014a), and the radial arm maze has probably been the most well used of them all when it comes to assessment of spatial working memory. Procedures involving delays or trial-unique stimuli have to be used to test working memory in these spatial navigation tasks (e.g., (Penley et al., 2013; Singer et al., 2013), but it is unclear whether these approaches test exactly the same processes assessed in human studies. For instance, rodent spatial working memory tasks may depend more on processes of short-term habituation than the "short term maintenance and manipulation of information in the absence of sensory input".

7. Conclusions

Throughout this review, and more widely in the accompanying papers contained in this special issue, it can be seen that attempting to provide a quantitative approach to the stratification of neuropsychiatric disorders is complex. Despite this, it is an initiative that is both timely and arguably vital to future clinical management of affected patients. The overall project that this review forms a part of is the product of several previous threads of scientific endeavour. Amongst these is the influential RDoC initiative (Insel et al., 2010), that significantly stimulated the neuroscience community to investigate new research domains irrespective of classical diagnostic boundaries of disease. The PRISM project has been cited as a leading example of how to operationalize the research domains concept (Insel & Cuthbert, 2015). Traditionally, however, many reviews that are framed within an existing diagnostic framework provide a highly detailed dissection of a specific psychological process within a limited scope of disease. As the explicit aim of PRISM is to explore new research domains and to offer innovation related to diagnostic frameworks, this requires a different level of detail. This review therefore set out to both provide a summary of the science within the remit of the project, but also to provide a description of how in this case the test selection process was performed to best achieve the outcome required.

To begin, an overview of the definition and utility of the terms attention and working memory confirmed that though dissociable, the two processes share much in common. Control of attention is arguably a more fundamental process that by definition underlies most other aspects of cognition. Working memory emerges as a higher order process that depends upon attentional capacity, but also requires the need to maintain and manipulate information over time that may potentially alter behaviour in the future. There is a great deal of overlap in the neuroanatomical substrates that subsume attention and working memory processes, but also some important differences depending on the particular sub-domain of function under consideration. For example, working memory processes will recruit other neural substrates in the brain depending on the quality of the information to be manipulated (e.g. phonological versus spatial).

Having made a draft decision to explore the cognitive domains of attention and working memory it was next important to establish whether these processes are implicated in both diseases. There emerges good evidence for deficits in attentional function being complicit in both SCZ and AD. Indeed, deficits in attentional control or sustained attention are hypothesized to be key drivers underlying positive symptoms in schizophrenia. In terms of neural substrates, a role for impaired frontal function (i.e. “hypofrontality”) is also implicit in several explanations of the pathophysiology of the disorder. While working memory can undoubtedly be impaired in SCZ, it is perhaps not always considered as such a cardinal feature of SCZ as it is for AD. Neither attentional nor working memory impairment is a necessary or sufficient element to diagnose SCZ or AD, although working memory deficits are a very likely fundamental cause behind the emergent symptoms used to define the onset of probable Alzheimer’s disease. Though there are several aspects of mnemonic function that are associated with characterization of probable AD patients, spatial working memory emerges as being of particular interest. It is often an early cognitive domain impaired in AD, which correlates well with the finding of significant pathology in the hippocampus early in the development of the disease. Spatial working memory is also an attractive domain to consider from the perspective of translational research, as such non-verbal mnemonic functions have clearer homologues in rodents. Altogether, there appears to be accord that the selection of these components of cognition (i.e. attention and working memory) give a reasonable chance of observing dissociable deficits in the two disease populations that may also inform as to some of the neural substrates involved.

The aim of PRISM is not simply to systematically assess attention and working memory processes across SCZ and AD, but to consider how these parameters in the context of a broader phenotypic battery may explain the spectrum of social withdrawal observed across patients irrespective of initial diagnosis. The domain of social cognition, and social withdrawal itself, is clearly of great importance to a number of neurological and psychiatric disorders (World Health Organization, 2008). Consistent with a research domains hypothesis, symptoms of social withdrawal have been demonstrated to be partially independent from other deficits in each disease, suggesting potential for a partial shared transdiagnostic pathway affecting neurobiological substrates which sustain social functioning (for detail, see Porcelli et al., 2018). Somewhat at contrast from a neuropsychological perspective, however, is the finding that both and attention and working memory function can modulate normal interpersonal behaviors (e.g., Bowie et al., 2008; Vlamings et al., 2010). Several lines of evidence also suggest that attention and working memory, by modulating social functioning, may determine social impairment in disease. These effects therefore could be quite independent from more proximal effects of either disease on social cognition. Critical and conclusive review of this field is very difficult at present due to the mixture of theoretical stances adopted, the broad range of tests used to assess cognition, and lack of systematic assessment across disease populations.

Finally, the operational restrictions of needing to deploy cognitive tests effective in broadly quantifying attention and working memory in a wide-ranging phenotypic battery were considered. No single task, or even a limited number of tasks, will be able to completely characterize such broad and heterogeneous constructs as attention and working memory. The intention was to make sure that chosen assays had the potential to index deficiencies in all of the broadly recognised subcomponents of attention and working memory as well as possible. From this point of view, the investigation of the neural substrates sustaining these deficits in the two disorders could highlight possible overlaps and differences between the effects of the two pathophysiological mechanisms on them, paving the way for the detection of possible therapeutic targets to improve these cognitive domains across disorders. Otherwise, assay choice was significantly influenced by patient burden, ability to incorporate electrophysiological or neuroimaging measures, and ability to offer a rodent homologue. Taking into account the considerations above, the attention sub-group nominated the Conners continuous performance test III, digit symbol substitution and attention network test, and the working memory group nominated n-back, complex span and spatial navigation/virtual environment tests. It was felt that these tests would offer the broadest measurement of attention and working memory sub-domains, yet not be too burdensome for patients under investigation. The concomitant investigation of the related domains of attention and working memory with specific and partially overlapping tests (e.g. CPT-III, which investigates some aspects of both attention and working memory), could be very helpful in deconstructing such complex processes. Some significant limitations are noted in the confidence associated with the provision of true rodent homologues of the clinical tests chosen, particularly for the domain of working memory.

Undoubtedly, the notion of measuring attention and working memory across these patient populations with the objective of determining a novel biological nosology is an incredibly challenging area to study with many pitfalls and criticisms. So far, little work has attempted to measure similar cognitive constructs across patient populations within the same study, and, to the best of our knowledge, no study has measured these basic cognitive domains in relationship with social functioning in different clinical populations. This investigation will hopefully pave the way for the development of novel treatments targeted at both social withdrawal and cognitive deficits in these patients.

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