Cognitive function in schizophrenia: Conflicting findings and future directions

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Published in:
Reviews in the Neurosciences

DOI:
10.1515/revneuro-2015-0060

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DOI 10.1515/revneuro-2015-0060
Received October 25, 2015; accepted November 16, 2015

Abstract

Introduction: Schizophrenia is a severe mental disorder with multiple psychopathological domains being affected. Several lines of evidence indicate that cognitive impairment serves as the key component of schizophrenia psychopathology. Although there have been a multitude of cognitive studies in schizophrenia, there are many conflicting results. We reasoned that this could be due to individual differences among the patients (i.e. variation in the severity of positive vs. negative symptoms), different task designs, and/or the administration of different antipsychotics.

Methods: We thus review existing data concentrating on these dimensions, specifically in relation to dopamine function. We focus on most commonly used cognitive domains: learning, working memory, and attention.

Results: We found that the type of cognitive domain under investigation, medication state and type, and severity of positive and negative symptoms can explain the conflicting results in the literature.

Conclusions: This review points to future studies investigating individual differences among schizophrenia patients in order to reveal the exact relationship between cognitive function, clinical features, and antipsychotic treatment.

Keywords: attention; cognition; dopamine; learning; schizophrenia; working memory.

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Introduction

Schizophrenia: positive and negative symptoms

Schizophrenia is a psychiatric disorder that can involve both positive symptoms (such as delusions and hallucinations) and negative symptoms (such as apathy, avolition, and social withdrawal). In addition to psychiatric dysfunction, most schizophrenia patients have cognitive impairments (Cohen et al., 1999; Abi-Dargham et al., 2002). The cause of these symptoms has been, in part, attributed to a dysregulation of dopaminergic signaling (Meisenzahl et al., 2007). Due to the heterogeneous nature of the disorder (Carlsson et al., 2001), schizophrenia may indeed be a dysfunction of multiple neural systems, varying among individuals. This paper focuses on dopaminergic dysfunction in an effort to provide a clear illustration of the main confounding elements that currently limit our understanding of the cognitive deficits experienced by patients with schizophrenia.

Over the last few years, several studies have shown that the nature of the cognitive impairment in schizophrenia depends on the degree to which negative symptoms are present, that is, whether the patients are of the deficit or nondeficit subtype (Farkas et al., 2008; Polgar et al., 2008; Somlai et al., 2011). For example, neuropsychological studies have shown that negative symptoms in schizophrenia are correlated with performance in frontostriatal-based tasks, such as probabilistic category learning (Farkas et al., 2008; Keri, 2008; Polgar et al., 2010). Importantly, many conflicting results obtained previously in the field may

have been a consequence of lumping different subtypes of patients together, so that important dimensions of individual variability were masked. For example, the degree of severity of negative symptoms among patients varies widely, leading to an often used dichotomy between non-deficit schizophrenia, in which only positive symptoms are present (with no or minimal negative symptoms), and deficit schizophrenia, in which both positive and negative symptoms occur (Carpenter et al., 1988).

Importantly, neural studies show that positive and negative symptoms are associated with changes to different neural regions and neurotransmitters (Lynch, 1992), thus suggesting that severity of these symptoms may differently impact cognitive function in schizophrenia. For example, some studies show that positive symptoms in schizophrenia result from a hyperdopaminergic activity in the hippocampus (for experimental support, see Krieckhaus et al., 1992; Tamminga et al., 2010; Zierhut et al., 2010) or hippocampal dysfunction (Bogerts et al., 1985; Laruelle et al., 1999; Weinberger, 1999; Goldman and Mitchell, 2004; DeRosse et al., 2007; Keri, 2008; Kessler et al., 2009; Mikell et al., 2009; Grace, 2010; Kegeles et al., 2010). Other studies suggest that dopaminergic alterations in the basal ganglia underlie the occurrence of positive symptoms (Kessler et al., 2009; Laruelle et al., 1999; Mikell et al., 2009; Kegeles et al., 2010).

Unlike positive symptoms, some studies show that negative symptoms may arise from a hypodopaminergic activity in the prefrontal cortex (Davis et al., 1991; Dassa et al., 1995; Okubo et al., 1997; Heckers et al., 1999; Monteleone et al., 2002; Guillin et al., 2007). For example, using PET scan, Okubo et al. (1997) found that lower dopamine levels in the prefrontal cortex correlate with the severity of negative symptoms in schizophrenia patients (for a similar finding, see Abi-Dargham, 2003). Research has also shown that the basal ganglia is generally intact in patients with minor negative symptoms (Okubo et al., 1997). There are a number of indications that D1 receptors in the prefrontal cortex are not properly activated in schizophrenia. Cortical dopamine neurons are significantly diminished in schizophrenia when compared with healthy controls (Okubo et al., 1997; Akil et al., 1999). These findings consistently correlate with the severity of negative symptoms of schizophrenia (Okubo et al., 1997; Goldman-Rakic et al., 2004; Javitt, 2009).

Antipsychotics

The use of antipsychotics has been shown to result in a reduction of symptoms in schizophrenia (Meisenzahl et al., 2007). Different atypical antipsychotics have dissociable effects on brain and cognition (Breier et al., 1999; Beninger, 2006). Some argue that most antipsychotics are used to treat psychiatric impairment, including positive symptoms, in schizophrenia, possibly by blocking dopamine receptors in the striatum or hippocampus (Klemm et al., 1996; Risch, 1996; Fink-Jensen, 2000; Rueter et al., 2004; Horacek et al., 2006). Many studies show that some antipsychotics are not effective at treating negative symptoms (Buckley and Stahl, 2007). However, other studies found that different antipsychotics have dissociable effects on positive and negative symptoms. For example, it was shown that clozapine is effective in treating both positive and negative symptoms (Kane et al., 1988; Fitton and Heel, 1990; Miller et al., 1994; Rosenheck et al., 1997), while risperidone was shown in some studies to be efficient in ameliorating negative symptoms only (Schooler, 1994; Tamrakar et al., 2006; Curtis et al., 2008). In contrast, other studies showed no difference between these two treatments in their effect on negative symptoms (Bondolfi et al., 1998; Breier et al., 1999; Asenjo Lobos et al., 2010). Other studies have found dissociable effects of different typical (or atypical) antipsychotics or typical vs. atypical antipsychotics on cognition (Meltzer et al., 1999; Shirazi-Southall et al., 2002; Fujimaki et al., 2012).

Antipsychotics have a non-uniform effect on cognition in schizophrenia patients such that they might enhance, impair, or have no effect on cognition, depending on the cognitive task employed and the specific drug used (Stip, 2006). One mechanism through which antipsychotics ameliorate cognitive dysfunction and symptoms in schizophrenia is by arguably targeting and blocking dopamine receptors (Seeman and Ulpian, 1983; Farde et al., 1988; Leysen et al., 1988; Wiesel et al., 1990). For example, studies have shown that antipsychotics enhance performance in latent inhibition (Feldon and Weiner, 1991; Dunn et al., 1993; Moser et al., 2000; Schmajuk et al., 2000) and acquired equivalence tasks (Shohamy et al., 2009) but generally not working memory (WM) (Castner et al., 2000; Snyder et al., 2008), as we will discuss in detail below. In addition, unlike second-generation antipsychotics, first-generation antipsychotics are more associated with impaired feedback learning (Bedard et al., 2000; Purdon et al., 2003; Paquet et al., 2004; Scherer et al., 2004).

Antipsychotic medications are ineffective in about 30% of patients with schizophrenia (Jones, 2004), leading to a class of patients known as treatment-resistant schizophrenia patients. de Bartolomeis et al. (2013) revealed that treatment-resistant schizophrenia patients perform significantly worse on the verbal memory test in the Brief Assessment of Cognition in Schizophrenia, and

this cognitive impairment was associated with higher severity of negative symptoms. Another study (Bourque et al., 2013) demonstrated worse visuospatial processing in treatment-resistant schizophrenia patients receiving clozapine when compared to non-treatment-resistant schizophrenia patients. Therefore, it has been proposed to include cognitive impairment and global functioning in definitions of treatment-resistant schizophrenia (Keefe and Fenton, 2007).

Cognitive performance in schizophrenia

There are ample studies of cognitive dysfunction in schizophrenia. The majority of cognitive paradigms used with schizophrenia patients are related to learning, WM, and attention (which we review below). Most of these studies, however, have found conflicting results, such that some studies report impaired or same function compared to controls. The goal of this review is to highlight these conflicting results for each cognitive domain in order to allow for future experiments to clearly understand the clinical factors that may impact cognition in schizophrenia.

Learning

There are many studies that have investigated learning performance in patients with schizophrenia (Waltz et al., 2007; Somlai et al., 2011; Weickert et al., 2013a,b), using reinforcement learning, probabilistic category learning, and generalization tasks. Our literature review shows that the different reports on learning performance in schizophrenia can be explained by differences in task details, the nature of symptoms, and medication status of the patients.

Many studies have reported feedback learning deficits in schizophrenia (Waltz et al., 2007, 2011; Hill et al., 2013). These deficits may result from dopamine dysfunction in the basal ganglia and corticostriatal circuits (Waltz et al., 2007; Foerde et al., 2008; Shohamy et al., 2008). Dopamine neurons project to areas of the brain responsible for motivation and reward learning (Schultz et al., 1997; D'Ardenne et al., 2008; Fiorillo, 2011) by coding prediction errors (Deserno et al., 2013). The dopamine theory has been used to explain the occurrence of aberrant reward learning in schizophrenia patients; if patients have a higher baseline dopamine level compared to controls, studies suggest that it may persist or elevate in probabilistic environments (Fiorillo et al., 2003; Preuschoff et al., 2006; Koch et al., 2010). The overabundance of dopamine may cause a saturation effect (Cohen et al., 2002), which would mean that any additional bursts would not signal prediction errors in a typical manner due to a reduced signal-to-noise ratio (Waltz et al., 2007). Therefore, Waltz et al. (2011) hypothesized that schizophrenia patients show a reduced ability to learn from phasic dopamine bursts, which also explain reward learning deficits (Waltz et al., 2007; Morris et al., 2008; Koch et al., 2010; Weickert et al., 2002, 2010).

In healthy participants, Koch et al. (2010) found a negative relationship between the uncertainty of feedback and dopaminergic activity in brain areas related to decision making and learning. In the same study, schizophrenia patients' performance in the reward probabilistic learning task was significantly impaired, and the patients did not exhibit decreased brain activation with increasing probability of reward as in healthy controls (Koch et al., 2010). The authors concluded that a reduction of brain activation during times of predictability conserves decision making and learning resources for tasks with greater uncertainty, thus making an individual more likely to make correct decisions. Conversely, patients with schizophrenia did not exhibit this reduction in brain activity, which leads to impaired learning performance. Furthermore, dopamine projected to the ventral striatum has also been implicated in reward learning (Pessiglione et al., 2006; MacDonald et al., 2011). For example, Morris et al. (2012) found abnormal dopamine activity in the ventral striatum in patients with schizophrenia compared to healthy controls. Waltz et al. (2011) found that schizophrenia patients showed diminished reward learning compared to controls by displaying an overall 'Go' bias while also showing a diminished ability to correctly select rewarding 'Go' choices. Thus, it was suggested that the elevated dopamine levels may be restricted to affecting dopamine D1 receptors (Waltz et al., 2011).

Not all evidence follows the findings by Waltz et al. (2011). For instance, recent evidence has indicated diminished punishment learning (and intact reward learning) in schizophrenia patients (Fervaha et al., 2013). These conflicting results may be due to medication effects, as the majority of the schizophrenia patient groups varied in their medication dosage and, therefore, it is difficult to dissociate medication from disease effects (Foerde et al., 2008). However, at least one imaging study has demonstrated dysfunctional dopaminergic activation in drug-naïve patients (Juckel et al., 2006). In another study, in chronic schizophrenia patients, it has been shown that verbal learning performance is correlated with positive and negative symptoms as well as antipsychotic dosage, suggesting that symptom and treatment status can

impact verbal learning abilities (Forbes et al., 2009). Also, one study in individuals with schizophrenia who were withdrawn from antipsychotic medication showed significantly improved probabilistic association learning (Weickert et al., 2013a,b). Studies found a significant positive correlation between antipsychotic medication dosage and reward learning (Nielsen et al., 2012).

It is also possible that task designs or assessment of learning in different tasks can explain the conflicting results on learning performance among schizophrenia patients. For example, some studies found that some learning does occur over many trials in conditions that have high probability ratios (Waltz et al., 2007) or in motor learning tasks that have deterministic rather than probabilistic reward values (e.g. see Scherer et al., 2003; Foerde et al., 2008), but see Weickert et al. (2002) for an alternative view. Weickert et al. (2013a,b) also found that patients can show impairment in early learning trials but improvement in later trials.

One of the most commonly used tasks to test learning is the weather prediction task, which measures probabilistic category learning performance. On every trial in this task, subjects are presented with a pattern of one to three cards and learn to classify each pattern of cards as being predictive of rain vs. sunshine, based on corrective feedback. Schizophrenia patients with severe negative symptoms show probabilistic category learning impairment using this task (Farkas et al., 2008). Experimental studies also found that not all atypical antipsychotics impair probabilistic category learning performance (Harris et al., 2009) and that some typical and atypical antipsychotics may have similar effects on weather prediction performance (Wasserman et al., 2012). These studies suggest that categorizing antipsychotics as typical vs. atypical may not explain learning performance, but perhaps affinity to dopamine receptors may better explain how antipsychotics impact learning performance.

Other studies have also investigated the generalization of learned rules in schizophrenia using the acquired equivalence task (Myers et al., 2003). This task has two phases: learning and generalization. In the learning phase, subjects learn to associate stimuli with responses, based on corrective feedback (e.g. A1→X1; A2→X1; A1→X2). In the generalization phase, subjects are tested on whether they have learned that stimuli become equivalent when they were previously associated with the same response (e.g. A1→?). The generalization phase includes two types of trials: retention and transfer. Retention trials are trials that were previously presented in the learning phase, whereas transfer trials include novel combinations of stimuli (see Myers et al., 2003). Several neuropsychological studies have shown that initial learning depends on the integrity of the basal ganglia, whereas generalization performance depends on the integrity of the hippocampus (Myers et al., 2003; Keri, 2008). It was found that while schizophrenia patients with severe negative and positive symptoms are impaired at both the learning and generalization phases of the acquired equivalence task, patients with positive symptoms but mild negative symptoms are only impaired at the generalization phase of this task (Farkas et al., 2008). Interestingly, Shohamy et al. (2009) found that the administration of antipsychotics to schizophrenia patients ameliorates their transfer generalization impairment. Research has shown that schizophrenia patients' performance on the acquired equivalence task is very similar to the performance of patients with mild Alzheimer's disease, hippocampal atrophy, and hypoxia (Myers et al., 2003, 2008; Bodi et al., 2009), suggesting a common hippocampal dysfunction in all these patient groups. It is possible that antipsychotics ameliorate hippocampus function and thus enhance generalization of learned rules (Shohamy et al., 2009), although this needs to be confirmed or disconfirmed by neuroimaging studies.

Working memory

WM is a complex form of short-term memory, where sensory information can be held and manipulated (Baddeley, 1981). WM dysfunction has been postulated to be a core feature of schizophrenia. It is said to be related to a formal thought disorder due to the inability to adequately retain recent ideas in memory, as well as negative and disorganized symptoms (Goldman-Rakic, 1994). It is suggested that WM deficits may explain attentional, executive, and learning difficulties in schizophrenia, as these processes also require maintenance and manipulation or transformation of information in memory (Elvevag and Goldberg, 2000; Collins et al., 2014). This suggestion is supported by functional neuroimaging studies, showing abnormal activation of the prefrontal cortex in tasks of executive function, attention, and WM (Manoach et al., 2003; Glahn et al., 2005). A systematic review and meta-analysis on WM function in schizophrenia comparing 36 cognitive tasks points to deficits in phonological, visuospatial, and central executive WM with no clear difference across domains or tasks (Forbes et al., 2009). Interestingly, WM deficits in schizophrenia patients are not simply explained by discrepancies in current general intellectual ability between patients and healthy controls (Forbes et al., 2009).

Using the Wisconsin Card Sorting Test, Malhotra et al. (2002) have shown that prefrontal dopamine function correlates with perseverative errors in this task in healthy subjects and schizophrenia patients (Bilder et al., 2002a,b). In this task, subjects are presented with four cards characterized by three dimensions: color, shape, and form of objects on each card. On each trial, subjects are given a card and instructed to categorize this card according to other cards presented. Subjects are not told the rule but learn the task based on feedback to their responses. Unknown to the subjects, the 'sorting' rules are shifted during the test, requiring subjects to learn to categorize cards based on new rules. Studies have found WM impairment in both medicated (Holmes et al., 2005) and unmedicated (Snyder et al., 2008; van Veelen et al., 2010) schizophrenia patients; this may be due to hypodopaminergic activity in the prefrontal cortex (Abi-Dargham et al., 2002). In agreement with the Wisconsin Card Sorting Test data, meta-analyses of cognitive performance have shown that WM impairment is one of the cognitive domains showing the greatest impairments in drug-naïve schizophrenia patients (Fatouros-Bergman et al., 2014) as well as in medicated patients (Lee and Park, 2005; Forbes et al., 2009). Other studies found that schizophrenia patients on atypical antipsychotics outperform patients on typical antipsychotics (Rossi et al., 2006).

The use of different WM tasks in the literature leads to some conflicting results. Importantly, the validity of comparing results between different types of WM has been called into question (Chapman and Chapman, 1973). Some tests, such as the forward digit span task, are associated with substantial heterogeneity, whereas others, such as verbal span task, are more homogenous (Forbes et al., 2009). Additionally, each WM task refers to different level of complexity and different cognitive subdomain of WM. Some tasks, such as the forward digit span, require only maintenance of information, while other tasks, such as digit span backwards, require additional manipulation of the stored information. Finally, as in Wisconsin Card Sorting Test, subjects have access to constant cues but, at the same time, are required to retain an underlying principle as well as feedback regarding prior responses (Perry et al., 2001). It has been suggested that in order to increase comparability of results between tasks, they should be matched for the level of difficulty and variance in scores among healthy control subjects (Chapman and Chapman, 1973). Along these lines, recently, we found that WM performance in schizophrenia patients depends on the WM task being employed (e.g. forward vs. backward WM span and short- vs. long-delay WM tasks) (Frydecka et al., 2014).

WM deficits in schizophrenia were found to be related to difficulty in goal maintenance, as observed in both medicated and unmedicated individuals at both acute and chronic stages of the illness (Javitt et al., 2000; Barch et al., 2001; Lee and Park, 2006). Similar deficits are shown in first-degree relatives of schizophrenia patients (MacDonald et al., 2003) and individuals with schizotypal personality (Barch et al., 2004; McClure et al., 2008). Additionally, goal maintenance in WM has been linked to the function of dorsolateral prefrontal cortex as well as its dopaminergic projections (Hazy et al., 2007), and its impaired activity has been repeatedly shown during WM tasks in patients with schizophrenia (Barch et al., 2001; Tu et al., 2006; Van Snellenberg et al., 2006). Furthermore, heightened sensitivity to distraction and proactive interference have been shown in patients with schizophrenia and their high-risk siblings (Brahmbhatt et al., 2006). On the other hand, it has been shown that patients with schizophrenia do not have difficulty in filtering irrelevant distractors before items entered WM (negative priming); however, they are impaired at the inhibition of irrelevant distractors after information had entered WM (proactive interference control) (Smith et al., 2011). In patients with schizophrenia, cue to inhibit items from WM is not followed by the reduction in ventrolateral prefrontal cortex activation typical for healthy control subjects (Eich et al., 2014).

The severity of negative symptoms was also found to impact WM performance in schizophrenia patients. When comparing studies with a longitudinal design, it has been shown that the degree of dysfunction in verbal WM among first-episode psychosis patients is significantly associated with negative symptoms (Bora and Murray, 2014). Similarly, by using the Wisconsin Card Sorting Test, it was shown that patients with severe negative symptoms are more impaired than patients without negative symptoms (Polgar et al., 2010).

Some other clinical factors have been associated with the severity of WM deficits in schizophrenia patients. The greater impairment in WM is observed in chronic schizophrenia patients in comparison to first-episode psychosis patients (Mesholam-Gately et al., 2009), and WM decline has been shown to correlate with illness duration (Forbes et al., 2009). Additionally, a recent meta-analytic study examining longitudinal changes in cognitive functioning has shown no decline of WM with time in schizophrenia patients (Bora and Murray, 2014).

Attention and latent inhibition

There are many studies of attentional dysfunction in schizophrenia (Schmajuk, 2001; Keedy et al., 2015).

Unlike some other cognitive processes, attention has been repeatedly linked to positive symptoms in schizophrenia (as discussed below). Attentional deficits have been also reported in the offspring of patients with schizophrenia (Diwadkar et al., 2011). Furthermore, attention training has been shown to improve treatment outcomes in schizophrenia patients (Silverstein et al., 2009), suggesting the close links between attention and schizophrenia symptoms.

Many studies argue that the up-regulation of dopamine and the correlated increase of perceptual salience cause the positive symptoms of schizophrenia (Kapur, 2003; Fletcher and Frith, 2009; Howes and Kapur, 2009; Kapur et al., 2005). For example, the attenuation failure hypothesis states that schizophrenia symptoms are putatively related to the inability to filter out (attenuate) perceptions of little or no importance, resulting in a tendency to make irrelevant observations (Gray et al., 1991a,b; Fletcher and Frith, 2009).

In 1979, Frith has, however, argued that schizophrenia may be understood as a shortage of perceptual attention (Frith, 1979; Joseph et al., 1979). Similarly, the attention deficit model of recurrent complex visual hallucinations (Collerton et al., 2005) argues for impaired attention in schizophrenia. Other studies have suggested the opposite – that schizophrenia is associated with an increase in attentional performance (Frith and Done, 1988, 1989; Kapur, 2003; Fletcher and Frith, 2009). One explanation for this conflict may be due to the broad operational definition of attention (Luck and Gold, 2008). This has resulted in a variety of paradigms used to study attention, with conflicting results due to differences in the procedures used (e.g. see Mushquash et al., 2012). Thus, it is relevant to identify the sub-types of attentional processes that are studied in order to unravel the specific nature of the attentional deficits in schizophrenia.

There are two modes of selective attention: top-down and bottom-up. Although top-down attention is deliberate, bottom-up attention to cues occurs because of difference in expectations (Friston, 2003; Coull, 2005; Stephan et al., 2009; Clark, 2013). Some studies reported bottom-up attentional deficits in schizophrenia (Neuhaus et al., 2011). On the contrary, other studies found that schizophrenia patients show deficits in top-down (but not bottom-up) attention (Sereno and Holzman, 1996). Studies suggest that dopamine plays a role in top-down more than bottom-up attention (Buschman and Miller, 2007; Noudoost and Moore, 2011; Schneider et al., 2015). It is possible that bottom-up attentional deficits are related to a non-dopaminergic dysfunction in schizophrenia. To our knowledge, this was not tested in schizophrenia, but future research should test this hypothesis.

Interestingly, many studies have shown that patients with schizophrenia show facilitated attention compared to healthy controls. One paradigm used to show this effect is known as the inhibition of return (Sapir et al., 2007; Mushquash et al., 2012). Inhibition of return describes a phenomenon where cue detection speed and accuracy are inhibited after orienting to a target, which is suggested to assist in the filtering of uninformative stimuli (Mushquash et al., 2012). It is this filtering that has been shown to be diminished in schizophrenia patients (e.g. see Gouzoulis-Mayfrank et al., 2004, 2007; Sapir et al., 2007). The reliability of these findings may be questionable, as the extent of the inhibition of return deficit fluctuated depending on the procedures used (Mushquash et al., 2012). However, the inhibition of return deficit has been found in unmedicated patients (Gouzoulis-Mayfrank et al., 2007) and has also been shown to be independent of medication dosage (Sapir et al., 2007). Thus, it can be argued that the diminished inhibition of return found in schizophrenia patients may be due to a dopamine dysregulation and may also be linked to psychosis (Gouzoulis-Mayfrank et al., 2007).

Along these lines, some other studies using different paradigms found increased attentional performance in patients with schizophrenia. For example, Morris et al. (2013) found increased attention to irrelevant cues correlated with positive symptoms in schizophrenia. Furthermore, other recent studies found enhanced voluntary attention in schizophrenia (Spencer et al., 2011). This enhanced attentional facilitation is attributed to maladaptive prediction errors. Prediction errors signal the difference between what is anticipated and what occurs in the environment. Smaller predictor errors signal enhanced predictive values for a given cue and thus further facilitate attention. It has been argued that an overabundance of dopamine in schizophrenia patients attenuates these prediction errors and thus results in an increase of attention to irrelevant cues (Corlett et al., 2007; Spencer et al., 2011; Morris et al., 2013), which can then increase psychotic episodes in the patients.

As attention imbalance theories have developed, they have been tentatively linked to dopamine dysfunction through its function as a moderator of perceptual saliency, which arguably causes the positive symptoms of schizophrenia (Kapur, 2003; Kapur et al., 2005; Schwartz et al., 2005; Howes and Kapur, 2009; Heinz and Schlagenhauf, 2010) and the negative symptoms as well (Golembiewski, 2013). A salient event is a perception that is marked as being of importance relative to other percepts. An increase in dopamine levels in schizophrenia may

increase attentional performance independently of cue and context (Kapur et al., 2005). Aberrant saliency is presumed to cause disorganized thoughts, hallucinations, and subsequent delusions. According to Fletcher and Frith (2009), people get so used to normality that they fail to notice it, while in schizophrenia, attenuation fails so that normal experiences appear salient. The concept of salience is based on the assumption that we selectively attend to a limited number of competing streams of information by filtering out irrelevant information (Milstein et al., 2005). In this framework, saliency is the measure of the influence that a cue has in gaining attention. Along these lines, Kapur et al. (2005) hypothesize that 'the normal process of context-driven novelty and salience attribution is usurped by an endogenously driven assignment of novelty and salience to stimuli… without cue or context'. One hypothesis is that a psychotic episode is caused by a functional over-availability of dopamine or D2 receptors (Laruelle and Abi Dargham, 1999), which arguably increases attention saliency.

The latent inhibition task is used to test the ability to filter out irrelevant stimuli, a process that is of relevance to schizophrenia symptoms. Latent inhibition refers to the retarded cue-feedback acquisition that follows unreinforced exposure to the cue alone (Lubow, 1973). In the first phase of the task (exposure phase), some subjects (exposed condition) will hear an auditory stimulus (conceptually, the cue, or conditioned stimulus) embedded in an auditory masking task; for the other subjects (nonexposed condition), the masking task is delivered alone. In the second phase of the task, all subjects are required to learn to associate the auditory stimulus with a visual screen event (conceptually, the feedback, or unconditioned stimulus). Lubow (1973) found that those in the exposed condition learned the association slower than did participants in the nonexposed condition. One interpretation of these findings, offered by Lubow and colleagues, is that latent inhibition reflects conditioned inattention; during the exposure phase, participants learn that the static stimulus does not predict any salient event, and so attention to it is decreased. This reduces the ability of that stimulus to enter into subsequent associations, retarding acquisition of the static-increment association and producing latent inhibition (Lubow, 1989).

Among a group of individuals with acute schizophrenia, the stimulus-response acquisition occurred at the same speed regardless of prior exposure to the stimulus (Baruch et al., 1988). Also, Becker et al. (2003) found that latent inhibition is disrupted in schizophrenia. Latent inhibition was similarly disrupted in a group of college students who scored above the median on psychological scales indexing psychotic proneness (Lubow, 1992) and in a group of normal participants administered a single dose of amphetamine (Gray et al., 1992), a dopaminergic agonist that induces behavioral symptoms mirroring some of the attentional impairments in schizophrenia (Gray et al., 1991a,b). In brief, individuals with schizophrenia (or humans or animals administered with dopaminergic agonists) have been shown to be less able to reduce attention to the stimulus during the exposure phase and accordingly show no impairment in forming associations involving that stimulus later (Swerdlow et al., 1996; Kathmann et al., 2000; Lubow et al., 2000; Rascle et al., 2001), although this has not always been found (Swerdlow et al., 1996). Moreover, it has been suggested that altered latent inhibition performance in schizophrenia might be attributed to antipsychotic medication normalizing behavioral function in the patients (Williams et al., 1998); indeed, patients with chronic schizophrenia may be less different from controls compared with patients with acute schizophrenia. It is important to note that other studies on schizophrenia did not find the latent inhibition effect (Martins Serra et al., 2001). It is suggested that increased dopamine levels in the hippocampus (as in schizophrenia) disrupt latent inhibition. Studies have shown that positive symptoms in schizophrenia are associated with disrupted latent inhibition (Gray et al., 2002; Burch et al., 2004; Evans et al., 2007; Schmidt-Hansen et al., 2009). Our modeling framework (Moustafa and Gluck, 2011) suggests that by decreasing dopamine levels in the hippocampus, antipsychotics normalize hippocampus function and thus enhance performance in latent inhibition, as found in experimental studies (Dunn et al., 1993; Moser et al., 2000).

Many studies found that antipsychotics can effectively treat attentional deficits in schizophrenia (Serper and Chou, 1997; Keedy et al., 2015). For instance, one study found that antipsychotic medications reversed the attentional facilitation found in schizophrenia patients (Sapir et al., 2007). However, meta-analyses studies found that atypical antipsychotics do enhance attentional performance, possibly by normalizing dopamine function in the caudate nucleus (Keefe et al., 1999). These conflicting findings can possibly be due to the different antipsychotics used in these studies.

Conclusion

This review highlights the complex relationship between clinical symptoms, antipsychotics, and cognitive

symptoms in schizophrenia. As discussed above, we found that the type of cognitive domain being tested, medication state, the dose and kind of antipsychotic medication used, as well as clinical features of the patients (positive and negative symptoms) can explain the conflicting results in the literature.

Most previous neuropsychological studies of schizophrenia ignore the differences in the severity of negative and positive symptoms among the patients; they mainly compare patient performance (as one group) to matched controls. Ignoring individual differences among schizophrenia patients (and the nature of their medications) could lead to conflicting results. For example, as discussed above, some studies have shown that schizophrenia patients are impaired at probabilistic category learning (Waltz et al., 2007; Murray et al., 2008), but others did not report any probabilistic category learning impairment (Somlai et al., 2011). A similar conflict is seen in the literature, with some studies reporting (Goldman-Rakic, 1994; Cohen et al., 1999) but others not reporting (Gold et al., 2006) WM impairment in schizophrenia. We suggest that some of these conflicting results may have arisen from a failure to address individual differences due to patient heterogeneity as well as different medications administered to the patients at the time of cognitive testing.

There are studies showing that a reduction in symptoms contributes to cognitive improvements. Interestingly, it has been shown that reduction in negative symptoms is associated with improvement in WM and executive functions, while improvement of positive symptoms has been linked to the better visual memory performance in the meta-analysis of first-episode psychosis patients (Bora and Murray, 2014). In chronic schizophrenia patients, there is consistency in documenting an association between negative symptoms and severity of executive functions, while positive symptoms are related to specific neurocognitive functioning with less consistency (Reichenberg, 2010).

The majority of studies have been conducted in drug-treated patients, thus it remains unclear if cognitive deficits in schizophrenia can be solely attributed to the underlying disorder or, to some degree, represent an effect of antipsychotic treatment (Fatouros-Bergman et al., 2014). Atypical antipsychotics are considered to improve cognition (Weickert and Goldberg, 2005), while typical antipsychotics do not (Bilder et al., 2002a,b; Woodward et al., 2005), and some studies did not confirm these findings (Keefe et al., 2007a,b). Moreover, it should be noted that long-term consequences of antipsychotic treatment might be detrimental to cognition. Progressive cognitive decline has been shown to correlate with antipsychotic medication dose both in nonhuman primates (Konopaske et al., 2008) and in patients with schizophrenia (Ho et al., 2011).

Even though cognitive deficits across all domains are present at early stage of the illness (Fatouros-Bergman et al., 2014), additionally, a factor of duration of illness should be taken under account when assessing cognitive functioning. It has been shown in the longitudinal brain imaging studies that there are numerous progressive brain changes in patients with schizophrenia, such as loss of cortical gray and white matter or lateral ventricular enlargement (Kempton et al., 2010; Olabi et al., 2011; Vita et al., 2012). These changes have been attributed to the disease progression, effect of antipsychotic long-term treatment, and decreased environmental stimuli related to social isolation (Bora and Murray, 2014). Consequently, there is a relative increase of patient-control cognitive differences with age (McIntosh et al., 2013).

The accuracy of the assessment of cognitive functions in schizophrenia and their main moderators is of great importance due to the fact that they may serve as a vulnerability marker of psychosis as well as prognostic marker for future functional outcome and quality of life indices.

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