Attentional window in schizophrenia and schizotypal personality: Insight from negative priming studies

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Abstract

One of the core deficits that characterizes schizophrenia is an increase in distractibility and disinhibition at all levels of information processing. Patients with schizophrenia seem unable to focus attention on the relevant events while ignoring the irrelevant stimuli. This pattern of behavior is also observed in unmedicated schizotypal individuals who may carry liability for schizophrenia. In this review, we focus on studies of attentional inhibition, as assessed by the negative priming paradigm, to elucidate the relationships among deficits in inhibition, clinical symptoms and medication effects. We then consider models of the etiology of deficits in negative priming in schizophrenia and schizotypal personality. Finally, we discuss the potential power of utilizing hypothesis-driven cognitive paradigms in psychiatric research.
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1. Introduction

An inability to focus on the relevant stimuli while simultaneously ignoring the irrelevant stimuli is a cardinal feature of acute schizophrenia (McGhie & Chapman, 1962; Shakow, 1962). Patients with schizophrenia display weakened inhibition in a wide range of tasks (please see the introductory article in this special issue and Appendix A for definitions of the tasks): impaired sensory gating (McDowd, Filion, Harris, & Braff, 1993), reduced prepulse inhibition (Braff, Grillon, & Geyer, 1992), reduced latent inhibition (Baruch, Hemsley, & Gray, 1988), diminished Kamin blocking effect (Jones, Gray, & Hemsley, 1992), increased interference on the Stroop task (Carter, Mintun, Nichols, & Choen, 1997), increased errors on the anti-saccade task (Fukushima et al., 1988), and reduced or abolished negative priming (Beech, Powell, McWilliam, & Claridge, 1990; Park, Lenzenweger, Puschel, & Holzman, 1996). Disrupted inhibition allows irrelevant stimuli to intrude during information processing and disrupts goal-directed activities (e.g., Frith, 1992; Hemsley, 1987), thus contributing to the increased distractibility observed among schizophrenic patients. Such disruptions of inhibition can contribute to a wide range of cognitive and behavioral deficits as well as clinical symptoms

of schizophrenia (Gray, Feldon, Rawlins, Hemsley, & D, 1991). Therefore, understanding abnormalities of attentional inhibition in schizophrenia may be central to elucidating the core features of the disorder.

Intrusion of irrelevant stimuli into ongoing, goal-directed activities can occur temporally and spatially. If the task involves rapid information processing over time such as the continuous performance test (CPT) (e.g., Cornblatt, Lenzenweger, Dworkin, & Erlenmeyer-Kimling, 1985), "repetition blindness" (e.g., Kanwisher, 1987), or "attentional blink" (e.g., Raymond, Shapiro, & Arnell, 1992), irrelevant distractors can intrude into target events in vulnerable individuals (see Fig. 1). Susceptibility to such interruptions is believed to be elevated in patients with schizophrenia as well as in individuals who may be at risk for schizophrenia. Distractors can intrude into the "spotlight" of attention. This "spotlight" of attention in schizophrenic patients is hypothesized to be distended or magnified over space (see Fig. 2), which reduces ability to ignore or inhibit distractors. In healthy individuals, both spatial and temporal control of attention is flexible and context-appropriate. In other words, healthy individuals are able to modulate and adjust the size of the attentional window over time and space to meet the changing demands of the environment. Such flexibility may be lacking in schizophrenia. In other words, the attentional "window" of schizophrenic patients can be conceptualized as wide and broad. A broad attentional window allows distractors to intrude upon information processing, and it is possible that impaired

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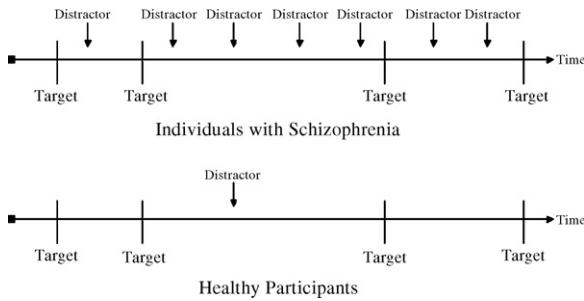 *E-mail address:* sohee.park@vanderbilt.edu (S. Park).

Fig. 1. Susceptibility to distractors over time. Compared to healthy controls, patients with schizophrenia are more susceptible to distractors intruding as they attempt to attend to targets presented in series. In contrast, healthy controls are more likely to block out irrelevant distractors.

inhibition may be a central factor in the broadening of the attentional window.

As noted in the introductory article of this special issue, attentional or cognitive inhibition can be assessed by a variety of paradigms. In this review, we focus on the *negative priming task*, which was originally developed to assess the inhibitory component of selective attention (see Tipper, 1985). Selective attention is thought to arise from at least two mechanisms: one involving an excitatory process associated with the target stimulus and the other involving an inhibitory mechanism that is associated with the ignored stimulus (e.g., Neill & Westberry, 1987). The negative priming (NP) paradigm typically involves two stages. First, the participant is asked to select a target while ignoring distractors in the 'prime' display, thus the participant is exposed to irrelevant stimuli that are to be ignored. When a stimulus is successfully ignored during a selective attention task, its internal representation is hypothesized to be inhibited and this inhibitory process is thought to influence subsequent behavior. In the second stage ("probe" display), the previously ignored stimulus is presented as the target to be selected. One important consequence of such inhibitory influences is that the subsequent selection of the previously ignored stimulus *increases* the response time (RT). This increase in RT underscores the influence of *latent* inhibition on current goal-directed behavior. NP is conceptually similar to the latent inhibition (LI) paradigm,
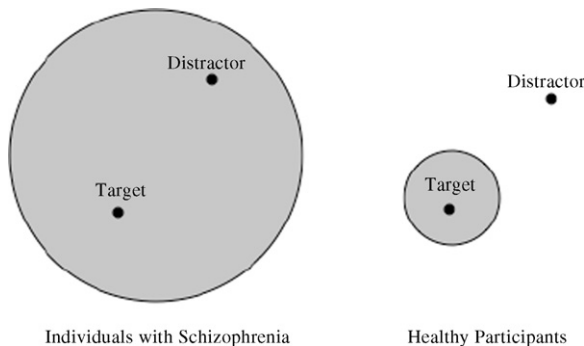
which refers to a process by which exposure to an ignored stimulus (e.g., a distractor) prevents or retards conditioned associations with that stimulus being learned at a later time. Both NP and LI tap into ability to focus attention while ignoring irrelevant features of the environment, and importantly they reveal the behavioral consequences of selective attention and inhibition on subsequent selection or learning. Thus, failed inhibition can lead to a 'better' performance later in that an inability to ignore a distractor will result in reduced or abolished NP and LI, which will be observed as faster RT. In other words, individuals whose attentional inhibition is reduced will therefore show a behavioral facilitation when they are asked to select or learn the distractor stimuli.

The past two decades have yielded an abundance of data and insight into the nature of attentional inhibition deficits in schizophrenia, and more specifically how these deficits relate to different clinical symptoms. Schizophrenic symptoms can be broadly subdivided into two factors: 'positive' and 'negative' (see Andreasen, 1983, 1984). Positive symptoms are characterized by hallucinations, delusions and thought disorder. Negative symptoms include poverty of speech, flat affect, anhedonia and anergia. Acutely psychotic schizophrenic patients with elevated positive symptoms, especially if they are unmedicated show reduced or abolished NP (e.g., Beech, Powell, McWilliam, & Claridge, 1989; Park et al., 1996; Park, Puschel, Sauter, Rentsch, & Hell, 2002), but normal NP is observed in medicated schizophrenic patients with low positive symptoms (Park et al., 1996, 2002). Anti-dopaminergic drugs seem to play a key role in treating positive symptoms and restoring inhibition (Beech et al., 1990). However, there have also been non-replications (e.g., David, 1995; Moritz, Jacobsen, Mersmann, Kloss, & Andresen, 2000). Conflicting evidence for abnormal NP in schizophrenia may be due to several sources of noise, including task-specific parameters, clinical symptoms/syndromes, and medication status. There is also debate about the putative cognitive mechanisms.

The present review aims to summarize and provide a cohesive explanation of these findings. We will first review the research on verbal and spatial negative priming effect before discussing the role of clinical symptoms and cognitive mechanisms that may support inhibition. We will discuss NP effects with respect to two groups of individuals: schizophrenic patients and individuals with elevated "schizotypal" traits. It is important to note that the latter group does not refer to those with DSM-IV Axis II Schizotypal Personality Disorder. Instead, these hypothetically psychosis-prone participants are ascertained psychometrically via self-report questionnaires that have been shown to be reliable and valid, such as the Perceptual Aberration-Magical Ideation Scales (Chapman, Edell, & Chapman, 1980) or the Schizotypal Personality Questionnaire (Raine, 1991) or the Oxford–Liverpool Inventory of Feelings and Experiences (Mason & Claridge, 2006). Since schizotypal individuals are not medicated but show mild signs of schizophrenia-like syndromes (see Raine, 1991), they provide a practical opportunity for observing behaviors without the confounds of studying chronically ill and medicated patients.

Fig. 2. "Spotlight" of attention–spatial. Spotlight of attention is "larger" in schizophrenic patients than in healthy controls, which allows both target and distractor to be processed.

1.1. Review of the negative priming effect in schizophrenia and schizotypal personality

In schizophrenia research, most studies have examined NP using Stroop-like and spatial localization tasks. While both tasks are visual, the localization paradigm requires a spatial representation of the stimulus and distractor, while the Stroop-type tasks requires semantic or lexical representation. We begin by discussing the findings from Stroop-type tasks assessing semantic NP, and then we discuss findings from the localization paradigm.

1.1.1. Verbal negative priming

In typical Stroop-like NP tasks, a color word stimulus is presented in a conflicting hue (e.g., the word *red* is printed in blue ink) during the prime trial. The participant is instructed to respond to the hue of the word rather than to the meaning of the word. In this case, the word meaning is the irrelevant distractor and must be inhibited, while the actual hue represents the relevant target. After an inter-stimulus interval, another word is presented (e.g., the word *green* printed in red ink). This is called the probe trial. If the hue of this new word was the distractor in the previous trial, an increase in RT is generally observed in healthy individuals (i.e., negative priming effect) (see Fig. 3).

Much evidence exists to support verbal NP deficits in schizophrenia and schizotypal personality. For example, Beech et al. (1989) used a Stroop-like interference paradigm to assess the negative priming effect in medicated schizophrenic patients. NP was reduced (but not abolished) in these patients. In a subsequent study, they also found that chlorpromazine, a dopamine antagonist, increased NP in healthy, normal individuals (Beech et al., 1990). In other words, antidopaminergic drugs seem increase inhibition. This result suggests that NP deficit may become normalized in medicated schizophrenic patients. Indeed, NP deficits were not observed in schizophrenia patients who were treated with antipsychotic medications (Salo, Robertson, Nordahl, & Kraft, 1997). In contrast, unmedicated, acutely psychotic schizophrenic patients (who are presumably

in a hyperdopaminergic state) do exhibit deficits in NP (see Gray et al., 1991). In addition, positive symptoms but not negative symptoms are associated with deficits in NP. (Peters et al., 2000) found diminished verbal NP among acutely psychotic patients using a Stroop-like NP task and concluded that positive symptoms rather than the diagnosis of schizophrenia modulate NP deficits. In sum, researchers have suggested that NP deficits are most apparent when positive symptoms are present, and are ameliorated by antipsychotic medications.

If antipsychotic drugs (i.e., dopamine antagonists) can restore NP to normal levels, it is necessary to examine NP in unmedicated individuals. As most persons with schizophrenia are medicated, one way to examine unmedicated samples is to study people with elevated schizotypal personality traits. Such studies can examine the relationship between schizotypal syndromes and NP in the absence of medication. There is considerable evidence supporting reduction of verbal NP effect in schizotypal individuals especially when positive syndromes are present (Beech & Claridge, 1987; Beech, McManus, Baylis, Tipper, & Agar, 1991; Beech et al., 1989; Moritz, Mass, & Junk, 1998). But Sturgill and Ferraro (1997) found that deficits in verbal NP was correlated with elevated schizotypal traits. In addition, there might be a sex difference in NP in relation to schizotypal traits. Steel, Hemsley, and Jones (1996) observed reduction in verbal NP in schizotypal subjects but only in males.

In sum, schizophrenic patients, especially during acute psychosis show reduced or abolished verbal NP. Such effects are diminished among medicated samples, but in addition, there is evidence for reduced verbal NP in healthy individuals with elevated schizotypal personality traits. One potential problem with NP tasks that require semantic representation is that schizophrenia is also associated with anomalous semantic networks (Kwapil, Hegley, Chapman, & Chapman, 1990; Manschreck, Maher, Milavetz, Weisstein, & Schneyer, 1988; Spitzer et al., 1994) and the hallmark of acute psychosis is formal thought disorder, which reflects underlying abnormalities of the semantic system (Manschreck et al., 1988; Siekmeier & Hoffman, 2002). Therefore, priming tasks that are dependent on appropriate semantic processing may not be ideal for schizophrenic patients, especially when they are floridly psychotic. NP tasks that typically have been used in schizophrenia research require language processing and articulatory responses, but language disturbances during the acute psychotic state may confound these measures of attentional and inhibitory abnormalities.
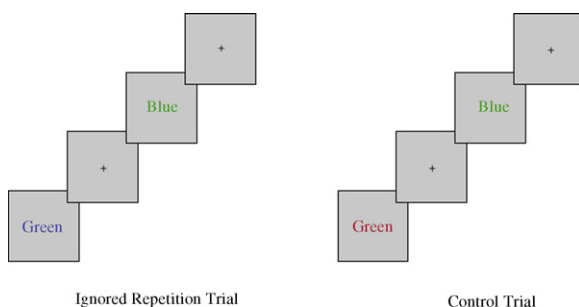

Fig. 3. Verbal/semantic negative priming task. In the ignored repetition condition, a previously ignored distractor feature (e.g., the meaning of the word) is the relevant target in the consecutive probe trial (e.g., the hue of the word is green). In the control condition, the distractor is not the target in the consecutive probe trial. Negative priming effect is calculated by subtracting the RT of the ignored repetition condition from the RT of the control condition. If the RT of the ignored repetition condition is greater than the RT of the control condition, the resulting RT difference will have a minus sign (i.e., negative). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

1.1.2. Spatial negative priming

Spatial NP tasks involve localization of visual targets and have important advantages compared with the verbal NP tasks. Many studies of schizophrenia that show cognitive deficits must address the fact that severely psychotic individuals tend to have a broad range of deficits. Thus it is possible that deficits in verbal NP may be due to generalized cognitive impairments of schizophrenic patients. Spatial NP tasks are easy; participants are asked to detect a target. Such simple tasks generate almost no errors, which allows researchers to interpret changes in RT without having to account for performance differences between
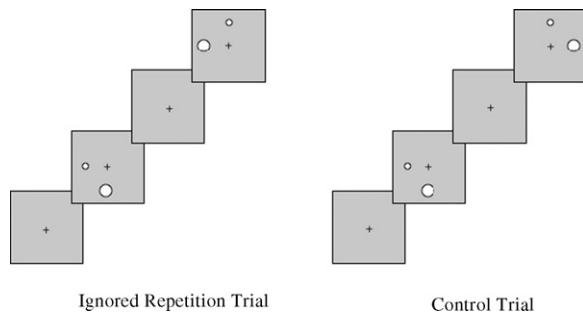
Ignored Repetition Trial   Control Trial

Fig. 4. Spatial negative priming task. In the ignored repetition condition, the target of the prime trial (e.g., the large circle) is presented with a distractor (e.g., small circle). In the consecutive probe trial, the target of the prime appears in the position previously held by the distractor. In the control condition, the target does not appear in the position held previously by the distractor. Negative priming effect is calculated by subtracting the RT of the ignored repetition condition from the RT of the control condition. If the RT of the ignored repetition condition is greater than the RT of the control condition, the resulting RT difference will have a minus sign (i.e., negative).

schizophrenic patients and healthy controls. Cognitive demands are low and therefore even floridly psychotic patients can perform this task without generating errors. Another advantage is that it is possible to compare non-verbal, attention task performance across species. Animal studies allow greater freedom in testing pharmacological effects and increase the potential for uncovering potential neurobiological mechanisms.

In a prototypical spatial NP task, a target stimulus and distractor are presented in different locations on a computer screen (see Fig. 4). The participant is instructed to ignore the distractor, while responding to the location of the target stimulus (prime trial). After an inter-stimulus period, the target stimulus and distractor appear (probe trial). If the current target location overlaps with the location of the previously ignored distractor in the prime trial, healthy controls demonstrate an increase in RT to the target. This increase in RT indexes the spatial NP effect. Because spatial NP minimizes the linguistic and cognitive demands, it can be used with a range of populations including children and psychiatric patients.

Spatial NP has been shown to be impaired in schizophrenia patients (e.g., Fuller, Frith, & Jahanshahi, 2000; Park et al., 1996, 2002; Vink, Ramsey, Raemaekers, & Kahn, 2005), specifically in acutely psychotic patients with elevated positive symptoms (Hoenig, Hochrein, Muller, & Wagner, 2002; Park et al., 1996, 2002). Furthermore, the level of spatial NP deficit was correlated with greater positive symptom severity in unmedicated acutely psychotic patients (Zimmermann et al., 2006). Park et al. (2002) investigated spatial NP in acutely psychotic schizophrenia patients at hospital admission, and followed them up 4 months later when their positive and negative symptoms were in partial remission. At baseline, spatial NP was reduced in schizophrenic patients with elevated positive symptoms but at the 4-month follow-up, spatial NP was intact. Normal spatial NP in medicated and stable schizophrenic patients was also observed by Jones, Cardno, Sanders, Owen, and Williams (2001).

Although much of the early research focused on the effects of antipsychotic medications as a whole, typical and atypical antipsychotic drugs may differ in their effect on attentional inhibition. Typical neuroleptic drugs achieve their antipsychotic properties by blocking dopamine D2 receptors where as atypical antipsychotic drugs act upon serotonergic receptors in addition to dopamine receptors (see Meltzer, 1989). MacQueen, Galway, Goldberg, and Tipper (2003) showed that schizophrenic patients taking clozapine, an atypical antipsychotic drug, had a significantly better spatial NP effect (i.e., normal inhibition) than did patients taking typical antipsychotic drugs. Clozapine-treated patients were shown to have a negative priming effect similar to control participants. Clozapine produces dopamine D2 and serotonin 5-HT2 receptor blockade and is more effective in alleviating negative symptoms than are typical antipsychotic drugs (Meltzer, 1989). It would be interesting to know whether clinical symptoms were better controlled in those who were on clozapine than those who were taking typical neuroleptics but the article by MacQueen et al. (2003) did not comment on this issue. That is, it remains unclear whether the benefits of atypical antipsychotic medication for spatial NP are related to the effects on clinical symptoms. This should be examined carefully in future studies.

As above, the potential medication confound can be circumvented by examining the relationship between NP and schizotypal symptomatology. Studies of schizotypal personality have shown that spatial NP is reduced in unmedicated schizotypal individuals, especially among those with elevated positive syndromes (e.g., Beech et al., 1991; Moritz et al., 1998; Park et al., 1996; Watson & Tipper, 1997).

To summarize, spatial NP is reduced in schizophrenic patients (e.g., Fuller et al., 2000; MacQueen et al., 2003; Park et al., 1996, 2002; Vink et al., 2005; Zimmermann et al., 2006) but its effects may vary with positive symptom severity and medication. Conclusions, though, are somewhat tentative due to several issues in this empirical literature that make cross-study comparisons difficult. Clinical symptoms of the patients vary widely across different studies. Many studies fail to report symptoms (e.g., Moritz et al., 2000). Moreover, very few studies have examined the effects of different types of antipsychotic medications carefully. Nonetheless, studies of schizotypal personality suggest that anomalous NP can occur in the absence of psychotropic medications (Park et al., 1996; Watson & Tipper, 1997) but it is unknown whether a subtle, internal dysregulation of the dopamine system in schizotypal subjects leads to abnormal NP.

1.1.3. Clinical symptoms and negative priming effect

Clinical symptoms of schizophrenia can be categorized into positive and negative symptoms (see Andreasen, 1983, 1984). A floridly and acutely psychotic patient usually displays both positive and negative symptoms but positive symptoms (e.g., hallucinations, delusions and thought disorder) are more easily detected than negative symptoms, which are characterized by absence of normal behaviors (e.g., reduced affect, poverty of speech, lack of will). Positive symptoms of schizophrenia have long been found to be associated with impaired inhibition (see Gray et al., 1991; Gray, Hemsley, & Gray, 1992; Peters et al., 2000). For example, differences between acutely psychotic and partially remitted schizophrenic patients have been found in the studies of NP (Park et al., 1996, 2002; Vink et al.,

2005), latent inhibition (Baruch et al., 1988), and Kamin blocking effect (Jones et al., 1992). In these studies, inhibition was reduced or abolished in acutely psychotic patients but restored or improved in chronic, partially remitted state. Reduced NP has also been observed in non-acutely psychotic schizophrenia patients, but the reduction of NP seems to depend on the positive symptoms (Fuller et al., 2000), and in general, positive symptoms are greatly increased during acute psychosis. Overall, these studies indicate that increased positive symptoms are associated with deficits in NP and since positive symptoms are greatly elevated during acute psychosis, abolition or reduction of NP tends to be observed during these episodes. Therefore, fluctuation of NP should be observed across time within individuals and at least one study (Park et al., 2002) has observed changes in NP over a course of 4 months but a future study with more observation points would greatly increase our understanding of the relationship between symptoms and NP effect.

While positive symptoms have been reported to be associated with NP deficit in schizophrenia, it is unclear whether this relationship is limited to schizophrenia. Since NP effect has not been studied systematically in relation to positive symptoms in other psychotic disorders, it is impossible to discern whether NP deficit during acute psychosis is specific to schizophrenia or to the positive symptoms themselves. If it were the latter case, bipolar patients during acute psychosis should also show deficit in NP. This case is a distinct possibility and should be tested.

A related issue is that of medication effect. Most of the studies we have reviewed above suggest that anti-dopaminergic drugs can increase and therefore improve attentional inhibition (MacQueen et al., 2003; Salo et al., 1997). Nonetheless, there is also evidence to the contrary (David, 1995) which could be consistent with a non-linear relationship between medication level and NP effects. To date, there is no dose–response data available to quantify this relationship. More research is urgently needed to clarify the medication effect on NP.

Examining the NP effect in healthy individuals with schizotypal personality can avoid the potential drug effects. As noted above, the presence of positive syndrome has been associated with reduced NP in schizotypal individuals (Park et al., 1996; Peters, Pickering, & Hemsley, 1994; Watson & Tipper, 1997) but the effects of a range of symptoms should be carefully examined.

To summarize, there is a consistent relationship between positive symptomatology and reduced NP in schizophrenia and schizotypal personality but the effects of antipsychotic drugs and other pharmacological agents on NP are not clearly understood. Since NP and other cognitive tasks could be used to quantify the degree of attentional impairments, a better understanding of pharmacological effects on NP could have the potential for significant clinical implications. Surprisingly, there has been very little effort to elucidate the relationship between pharmacological properties (e.g., neurotransmitter subtypes, pharmacokinetics, drug dose, etc.) and measures of attentional inhibition using NP. NP paradigm provides a behavioral instrument that could improve the precision with which we can assess the efficacy of drugs to treat attentional impairments. Furthermore, if the nature of NP deficits were more clearly understood, the extent of NP deficits might be used to predict treatment

response. But before this can become a practical reality, we need to be able to specify the relationships among clinical symptoms, pharmacology and NP and to elucidate the cognitive mechanisms that give rise to NP.

1.1.4. Mechanisms that support NP: inhibition versus episodic memory retrieval

A significant body of research has focused on the mechanisms that drive NP. The NP effect is independent of visual features of the ignored stimulus (Tipper & Driver, 1988), retinal locus (Tipper, Brehaut, & Driver, 1990), specific motor responses (Tipper, MacQueen, & Brehaut, 1988) and the modality of tasks (Tipper, Weaver, Cameron, Brehaut, & Bastedo, 1991). Therefore whether the task involves identification and naming of the target stimuli or just a simple spatial localization of the target, inhibitory processes seem to be activated as long as the distractor stimuli are successfully ignored. These findings also suggest that inhibition functions at a central level rather than at peripheral level. In addition, negative priming effect is robust and long-lasting (Tipper et al., 1991).

There has been a debate as to whether the negative priming effect is a consequence of inhibition or whether it involves episodic retrieval. May, Kane, and Hasher (1995) have suggested that inhibitory mechanism involved in NP do not aid current selection per se but prevent recently ignored information from regaining response access, thus facilitating coherent on-line processing. The episodic retrieval theory of NP hypothesizes that the presentation of a stimulus *automatically* induces the retrieval of the most recent episode involving that stimulus. The retrieved episode contains information about the stimulus, including the response that was made to it. Thus in this model, increased response time is caused by response competition between selecting the current stimulus and the memory of the previous ignored response made to that stimulus.

According to the inhibitory model of NP, the presentation of an item as a distractor results in the inhibition of that item, regardless of whether that item subsequently appears as a target. Therefore, according to this view when a stimulus is ignored, inhibition that is associated with that particular stimulus begins to builds up as soon as it is ignored. However, according to the episodic retrieval model, presentation of an item as a distractor has *no* consequences unless that particular item reappears on the subsequent trial, at which point, its representation as a distractor may conflict with the current response but this has nothing to do with inhibition.

May et al. (1995) suggest that episodic retrieval is induced when processing difficulties (e.g., target degradation) occur on probe trials, when the experimental context makes such a process advantageous (e.g., repeated target trials are included), or when the response task encourages post-lexical processes. Therefore to study inhibition in special populations such as schizophrenia patients, it would be important to rule out experimental conditions that may increase the likelihood of episodic retrieval. This suggests that spatial NP tasks that involve locating simple shapes may be more suited to probe attentional inhibition than verbal or semantic tasks. In addition, using stimulus displays that are long enough for participants to identify targets fully

and using easy response requirements that do not require post-lexical processing should insure that inhibitory mechanisms are engaged.

Closely related to the issue of inhibition versus episodic memory retrieval is the idea that perceptual mismatch, caused by target and distractor being perceptually distinct objects may determine NP (e.g., Park & Kanwisher, 1994). Moritz et al. (2000, 2001) have examined different aspects of the NP paradigms to determine the contribution of perceptual versus attentional deficits to NP by investigating the potential effects of backward masking, prime and probe presentation time, and stimulus-onset-asynchrony (SOA). Moritz et al. (2000) manipulated the response-to-stimulus interval (RSI) to determine if the NP effect was intact in schizophrenia but was maintained for a shorter period than healthy controls. If this were the case, NP investigated at shorter RSIs would not be impaired in schizophrenia. They tested the hypothesis that for a shorter RSI, NP would remain intact in both groups. In contrast to previous studies of chronic schizophrenia patients on antipsychotic medication (e.g., LaPlante, Everett, & Thomas, 1992; Park et al., 1996), they found that patients did not exhibit reduced NP in any condition. Unfortunately, the authors did not report symptom ratings nor medication status and therefore it is unclear whether the intact NP in these patients was due to the fact that they were asymptomatic and taking anti-dopaminergic medication. Intact (or even enhanced) NP effect has been reported in previous studies with chronic schizophrenia patients on antipsychotic medication (e.g., LaPlante et al., 1992; Park et al., 1996, 2002).

In a subsequent study, Moritz et al. (2001) tested the hypothesis that NP deficit in schizophrenic patients may stem from perceptual problems that prevent the patients from seeing the target. They used the visual backward masking paradigm in which an informational target stimulus is presented, followed after an interstimulus interval by a masking stimulus that interferes with or interrupts target identification. This technique can effectively prevent observers from perceiving the target. Moritz et al. (2001) examined the effects of using a mask in between prime and probe trials with the hypothesis that backward masking could trigger a perceptual deficit for schizophrenic patients as opposed to tapping an inhibition deficit. This study used a short and long presentation times (100 and 250 ms) with and without a mask. NP was reduced for schizophrenic patients in the 100 ms-with-mask condition but not in the other three conditions (Moritz et al., 2001). They concluded that the attenuation of NP for schizophrenia patients is observed only under special experimental conditions and is caused by an inability to perceive a briefly presented stimulus (Moritz et al., 2001). However, backward masking should affect both ignored repetition and control trials. In interpreting this reduced NP effect among schizophrenic patients for the 100 ms-with-mask condition, it is important to note that the RT for the neutral trials (808 ms) were significantly increased for this particular condition compared with the RTs for the neutral trials in the other three conditions (792, 775 and 780 ms). In contrast, the RTs for the ignored repetition conditions for schizophrenic subjects remained consistent across all four conditions (807, 809, 814 and 813 ms), regardless of stimulus presentation time (i.e., 100 or 250 ms) or the

presence of the mask. Beyond examining the RTs across conditions, it is important to consider the role of symptoms. While the authors reported a lack of correlation between symptom ratings and NP scores, they did not present the symptom scores so it is unclear whether these patients were in remission or not. This omission makes it difficult to interpret their results given that symptomatology may be central to reduced NP in schizophrenia.

Despite ambiguity in the above findings, the debate over inhibition versus perceptual explanation of reduced NP in schizophrenic patients seems to have been successfully addressed by Vink et al. (2005). They designed their task to remove potential perceptual mismatch and distractor salience, and still observed a NP deficit in schizophrenic patients. These results suggest that inhibitory abnormalities exert enduring and consistent influence on cognitive behaviors of schizophrenic patients, above and beyond other factors such as perceptual mismatch and episodic memory retrieval.

2. Discussion

In this paper, we reviewed the negative priming literature to better understand the extent and nature of attentional inhibition abnormalities in schizophrenia. Research suggests that the attentional window is figuratively wide open in schizophrenia, especially during acute psychosis. Persons with schizophrenia are unable to filter or inhibit irrelevant stimuli because both the target and the distractor are hypothesized to fall within the attentional spotlight. In addition, they are unable to inhibit distractors from intruding into target events across time. There is debate as to whether reduced NP effect in schizophrenia reflects reduced inhibition or the consequence of perceptual mismatch. But spatial NP tasks that are specifically designed to remove perceptual mismatch still result in NP deficit in schizophrenia, which suggests the presence of inhibitory impairments despite initial concerns as to whether the NP deficit in schizophrenia reflected inhibition or not. It is, however, possible that deficits in executive functioning in schizophrenic patients may further accentuate impairments of inhibition.

Abnormal attentional inhibition in individuals with schizophrenia is thought to be detrimental to ongoing information processing and to influence all aspects of behavior. This brings us to a practical question. How does one determine the degree of impairment in attentional inhibition that would presumably lead to other behavioral deficits? Is it possible to quantify the reduction of NP effect that would reliably predict other behavioral deficits? Without attempting to answer such questions, the utility of NP paradigms and the accompanying concept of attentional inhibition are not likely to be useful outside of the laboratory context. There is a need to apply what is known about attentional inhibition into a variety of clinical applications including cognitive rehabilitation, pharmacological trials, social training and even therapy sessions.

Although an expansive attentional window may be disruptive to a wide range of cognitive processes, there may also be subtle advantages. Failure to inhibit distractors does not necessarily pose a problem when the task at hand is to access all aspects of the current stimulus array or indirect associations among stimuli.

Being able to access information that may be deemed 'irrelevant' by most healthy individuals can be advantageous especially when divergent thinking or creativity is required. Indeed, there is evidence to indicate that reduced latent inhibition is linked to increased schizotypal personality traits and creativity in high functioning individuals (Carson, Peterson, & Higgins, 2003).

In this review, we summarized past research on negative priming effect in schizophrenia and schizotypal personality. There is strong evidence that schizophrenia is associated with reduced attentional inhibition and that this may be detrimental to ongoing information processing but many studies have produced conflicting information. It is clear that clinical symptoms (especially positive syndrome) and medication play a vital role in determining susceptibility for NP deficits. Acutely psychotic individuals with elevated positive symptoms tend to show a more pronounced NP deficit than chronic, stable patients in partial remission. In addition, the medication effect must be investigated systematically to find out which antipsychotic drugs are most effective in restoring NP and whether typical or atypical antipsychotic drugs have differential effects on NP. Moreover, it seems that spatial NP may provide a less "noisy" measure of NP in schizophrenia, as it does not involve the semantic or lexical processes that are known to be already impaired in this disorder.

Once the mechanisms that produce NP effect, possible pharmacological effects on NP, and the relationship between symptoms and NP are better elucidated, it will be possible to use the NP paradigm in clinical settings. NP tasks could be used as precise and effective tools in indexing attentional impairments to predict treatment response and to assess cognitive outcome for patients with schizophrenia. It is clear that hypothesis-driven, precisely designed experimental paradigms that can quantify behavior have enormous potential for increasing the effectiveness of treatment strategies in psychiatry. To realize this potential, improved communication and integration between basic and applied research programs are vital.

Acknowledgments

Appendix A. Brief descriptions of inhibitory tasks

A.1. Anti-saccade task

An oculomotor task where the participant is instructed to inhibit a reflexive saccade to a stimulus and, instead, to produce a saccade in the opposite direction.

A.2. Attentional blink (AB)

This phenomenon occurs when stimuli are presented in rapid succession. Participant is instructed to respond to two target stimuli. If the two target stimuli are presented very soon after the first target, the second one may not be perceived. This failure to perceive the second target, when it occurs closely following the first target is called the attentional blink.

A.3. Continuous performance test (CPT)

Task of sustained attention, during which participants are instructed to press a button when a letter A (cue) is followed by a letter X (target) in the CPT-AX version or when identical pairs of stimuli are observed (CPT-IP version). This process involves inhibition in that the stimuli must be ignored if they are not preceded by the task-appropriate cue.

A.4. Kamin blocking effect

This is an established animal learning paradigm measuring selective processing, in which reduced blocking reflects allocation of greater processing resources to non-relevant information. After learning stimulus "A" predicts reinforcement, a compound stimulus (A + B) is introduced with reinforcement. However, no learning occurs for stimulus "B" and B is not associated with the reinforcement. Thus, learning of "B" is said to be "blocked" by stimulus "A".

A.5. Latent inhibition (LI)

An inhibitory process by which exposure to an irrelevant stimulus, prevents conditioned associations with that stimulus being formed at a later time.

A.6. Prepulse inhibition (PPI)

This is a neurological phenomenon in which a weaker pre-stimulus (prepulse) inhibits the organism's reaction to a subsequent stronger stimulus (pulse), which normally elicits a startle response. The reduction of the amplitude of the startle as the result of the presentation of the prepulse reflects the ability to adapt to a strong sensory stimulus when a preceding weaker stimulus serves to warn the organism. The stimuli are usually acoustic, but tactile, visual and airpuff stimuli have also been used.

A.7. Repetition blindness (RB)

RB can be demonstrated during a rapid serial visual presentation of stimuli. When two identical targets are presented within the sequence within 200–500 ms of one another, participants fail to detect the second target. In other words, the participant is "blind" to the repeated target if an identical target has been previously presented within 200–500 ms.

A.8. Sensory gating

This is an adaptive selective attention mechanism by which the brain automatically adjusts its response to stimuli. It refers to the blunting of response to a second stimulus when it is presented very soon after the presentation of a first stimulus. It is very similar to PPI.

A.9. Stroop task

There are different versions of this task. In the color Stroop task, a word such as blue, green, red is printed in colored ink differing from the color denoted by the word's semantic meaning (e.g., the word "red" printed in yellow ink). Participants must ignore the meaning of the word and respond to the color of the ink. The Stroop effect refers to the slower reaction time observed when the meaning of the color word is inconsistent with the color of the ink in which the word is printed. The Stroop effect involves inhibition because the participant must inhibit the automatic response to read the word.

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