A meta-analysis of context integration deficits across the schizotypy spectrum using AX-CPT and DPX tasks

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Abstract:

Schizotypy and schizophrenia involve disrupted context integration (CI), the ability to assimilate internal and external information into coherent mental representations. Research has primarily examined patients with schizophrenia, with fewer studies assessing CI in schizotypy-spectrum groups. The literature shows overall CI deficits, but mixed results for specific performance patterns and associations with clinical symptoms. Furthermore, conclusions are limited by small samples and heterogeneity across studies. To examine CI deficits across the schizotypy spectrum using AX-Continuous Performance Task (CPT) and Dot Pattern Expectancy task (DPX) performance. Systematic review involved searching 4 databases and 12 journals, examining key references, and contacting 227 researchers for published and unpublished data. Search terms included AX-CPT/DPX/dot pattern expectancy task/CNTRACs/context integration/context processing and schizo/prodromal/high risk/psychosis; context and ultra high risk. Independent data from studies with diagnostically or psychometrically assessed schizotypy-spectrum groups and AX-CPT/DPX tasks with 10+ trials and 60+% AX trials were included. Articles were independently coded by two authors using predefined coding schemes with good agreement. Meta-analyses pooled outcomes using random-effects models. Forty-one studies met inclusion criteria. CI impairment was present across the schizotypy spectrum. CI deficits in schizophrenia were substantial and associated with disorganized and negative symptoms. Outcomes were comparable between patients with chronic and first-episode schizophrenia. At-risk groups demonstrated moderate CI impairment. Results were robust across task parameters and there was no evidence that reporting biases grossly impacted outcomes. Findings lend support to theories suggesting that CI is a stable vulnerability factor for schizophrenia.

Keywords: meta-analysis | schizophrenia | schizotypy | context integration | continuous performance task

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Article:

General Scientific Summary—The current study found that patients with schizophrenia have trouble keeping goals in mind related to contextual settings and circumstances. People at risk to develop schizophrenia have similar difficulty, but to a lesser degree. These results reveal a promising way to detect people at risk for schizophrenia early on, even before other symptoms of the illness appear.

Schizophrenia is the most severe manifestation of a continuum of symptoms and impairment known as schizotypy (e.g., Lenzenweger, 2010; Meehl, 1989). The schizotypy spectrum is heterogeneous and includes positive, negative, and disorganized dimensions. Positive schizotypy involves excesses and distortions in perception and thought content. Negative schizotypy involves diminished pleasure, social interest, thoughts, speech, affect, and motivation. Disorganized schizotypy involves impairment in the ability to regulate thoughts and actions, manifesting as odd speech and peculiar behavior (Kwapil & Barrantes-Vidal, 2015).

Schizophrenia as a Disorder of Disrupted Context Integration

Context integration (CI) is conceptualized as the adaptive, dynamic ability to assimilate internal information, such as task schemas, and external information, such as perceptual features of the environment, into a coherent mental representation (Barch et al., 2001, 2004; Cohen & Servan-Schreiber, 1992). Disrupted CI is implicated in the development of schizotypy and schizophrenia, with theoretical connections dating back to early phenomenological descriptions:

> I only saw fragments: a few people, a kiosk, a house. To be quite correct, I cannot say that I see all of that, because the objects seemed altered from the usual. They did not stand together in an overall context, and I saw them as meaningless details. . . . My impressions did not flow as they normally do. (Matussek, 1987, p. 92)

This account highlights the importance of context, which usually goes unnoticed but leaves a strange and fragmented world when disrupted. Early phenomenologists were influenced by Gestalt theory, which involves the tendency to perceive complete forms from individual visual elements (e.g., Wertheimer, 1912). Matussek (1952) and Conrad (1958) proposed that schizophrenic impairment in integrating individual stimuli within the perceptual context could contribute to delusion formation. This may occur as the dimming of the perceptual field causes stimuli to stand out, leading to attentional capture, feelings of uncertainty and anxiety, and ultimately, delusion as a means of restructuring the disorganized perceptual framework.

Modern theories emphasize a neural basis for impaired CI in schizophrenia. CI is proposed to occur at globalized cellular and perceptual levels (e.g., Phillips & Singer, 1997). Impaired coordination between bottom-up and top-down processing of contextual information may be associated with symptoms of schizophrenia (e.g., Silverstein & Schenkel, 1997). Phillips and Silverstein (2013) reviewed information suggesting that widespread disruptions in coordination between nearby neurons and across longer-range brain regions have been found in schizophrenia, and that these processes are related to CI impairment.

Impaired CI may not just be an outcome of schizophrenia, but may be an underlying mechanism contributing to cognitive, behavioral, and symptomatic manifestations of the illness (Barch & Braver, 2009; Cohen & Servan-Schreiber, 1992). CI is thought to underlie attention, working memory, and inhibition aspects of executive control. Thus, context representations serve as a top-down mechanism for focusing on task-relevant processes, and for maintaining and updating these representations over time (Barch & Braver, 2009; Barch & Sheffield, 2017). For example, poor representation and maintenance of context may manifest as behavioral symptoms such as disorganized speech resulting from failure to interpret a phrase's meaning from the broader context of a sentence or conversation (Cohen & Servan-Schreiber, 1992).

CI deficits are thought to involve impaired function in the dorsolateral prefrontal cortex (DLPFC) and its connection with other neural regions and neurotransmitter systems (see Barch & Sheffield, 2017). In line with these predictions, CI deficits are associated with diminished DLPFC activation and increased noise in the mesocortical dopamine system in empirical and computational studies (e.g., Barch et al., 2001; Braver, Barch, & Cohen, 1999; Lesh et al., 2013; MacDonald & Carter, 2003). In sum, phenomenological and neuroscientific theories of schizophrenia posit a key role of disruptions in CI at behavioral and neurological levels.

Measurement of Context Integration

There are several ways to measure CI, including tools designed to assess perceptual organization, linguistic, and cognitive measures of context processing. However, it is unclear whether "CI" assessed using these different measures involves the same processes. Research on perceptual organization in schizotypy-spectrum psychopathology often draws on Gestalt principles, using illusions to assess automatic tendencies to integrate visual features into a holistic perception. For example, people with disorganized schizotypy are less influenced than control participants by visual illusions in which the illusory perception requires intact context processing (Uhlhaas, Silverstein, Phillips, & Lovell, 2004). Another line of research employs sentence completion tasks to assess use of linguistic context (e.g., Chapman, Chapman, & Daut, 1976). For example, patients with schizophrenia perform worse than controls on tasks requiring them to complete ambiguous sentences. Namely, they tend to provide the common use of words rather than the unique use of words prescribed by the context of the sentence (Bazin, Perruchet, Hardy-Bayle, & Feline, 2000).

A third method for studying CI in schizophrenia uses cognitive tasks to measure ability to mentally maintain goals to guide behavioral responses to external stimuli (Barch & Braver, 2009). There are a variety of cognitive tasks that measure constructs similar to CI; however, the term CI has been used so broadly that it becomes unclear to what extent these tasks tap the same construct. Therefore, the current meta-analysis took a focused approach to examine CI as narrowly defined above. The cognitive tasks determined to best fit this conceptualization of CI are the AX-Continuous Performance Task (CPT; Servan-Schreiber, Cohen, & Steingard, 1996) and its nonverbal analog, the Dot-Pattern Expectancy task (DPX; Jones, Sponheim, & MacDonald, 2010; MacDonald, Goghari, et al., 2005). These tasks were selected because (a) they show strong construct validity (Barch et al., 2009), (b) they map on to neural mechanisms implicated in CI (Braver et al., 1999), (c) their design allows for examination of a specific deficit

in context processing—that is, greater impairment in CI compared with other areas of general cognition (Chapman & Chapman, 1973), (d) they have good psychometric properties, (e) there is a large body of literature using the tasks with schizophrenia-spectrum participants, (f) they were selected for inclusion in the Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia (CNTRACs) battery as cognitive neuroscience measures recommended for cross-cutting research in schizophrenia (Barch et al., 2009), and (g) synthesizing results from a single set of tasks ensures examination of a cohesive construct. Combining results from tasks assessing different cognitive processes could introduce noise to the data and lead to inconclusive or equivocal outcomes.

Expert consensus from the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) committee, which selected measures for the CNTRACs battery, was weighed heavily when considering tasks for the current meta-analysis. The CNTRICS committee chose the AX-CPT and DPX as the most appropriate measures of CI/goal maintenance. There are a number of similar tasks, such as probabilistic reversal learning, operation and symmetry span, preparing to overcome prepotency, and various Stroop tasks. However, these tasks were not selected as CI measures by the CNTRICS committee because they were deemed to lack construct validity, measure different aspects of executive control, are not widely used in schizophrenia research, or fail to differentiate specific cognitive impairment from generalized deficits (Barch et al., 2009; Carter, Minzenberg, West, & MacDonald, 2012). The present meta-analysis followed the CNTRICS determination and focused on AX-CPT and DPX tasks. The measures not included in this review have merit and utility, but were not considered appropriate for inclusion in the current meta-analysis.

The AX-CPT presents a series of single letters in rapid succession; an item pair is composed of two sequential letters, the cue followed by the probe. Participants must make a positive response when they see A followed by X (AX trials), and a negative response to other letter pairs: AY, BX, and BY, with B representing any non-A cue and Y representing any non-X probe. The AX-CPT assesses mental representation and maintenance of context by including a high proportion of AX trials to create a prepotent bias toward positive response when task goals are maintained (Henderson et al., 2012; Servan-Schreiber et al., 1996). The most common version involves 70% AX, 10% AY, 10% BX, and 10% BY trials. Response patterns are used to compute an index of overall sensitivity: d′context = z(AXhits) − z(BXfalse alarms), with lower d′context reflecting worse CI.

The DPX is a nonverbal variant of the AX-CPT that uses dot patterns instead of letters, which helps to minimize confounding verbal strategies. This variation sometimes involves a slightly different proportion of trial types (69% AX, 12.5% AY, 12.5% BX, and 6% BY trials). Performance on the AX-CPT and DPX correlate between .63 and .80 (Strauss et al., 2014), and both tasks demonstrate adequate internal consistency and test–retest reliability (Henderson et al., 2012; Jones et al., 2010).

A major benefit of the AX-CPT and DPX is that they allow researchers to examine a specific deficit in CI within a single task through examination of error patterns across trial types. Confirmatory factor analysis of both tasks showed that BX trials primarily load on a context-processing factor, AY trials load on a preparatory factor, and AX trials load on both factors

(MacDonald, Goghari, et al., 2005). BY trials check that participants understood and attended to the task. AY trials should be most difficult for individuals with intact CI who keep task goals in mind and prepare to respond when cued by A. BX trials should be most difficult for people with impaired CI because X triggers a response when the goal is not properly maintained (Barch & Braver, 2009). Two studies have shown a double-dissociation pattern, in which schizotypy-spectrum groups made more errors than control groups on BX trials but fewer errors on AY trials (Barch et al., 2001; MacDonald, Pogue-Geile, Johnson, & Carter, 2003).

Cue-probe delays can reveal processes related to maintenance of context. When CI is intact, BX accuracy should increase across longer delay periods because participants have more time to prepare a correct, nontarget response following the B-cue. In contrast, longer cue-probe delays should diminish AY accuracy in healthy participants because they have more time to prepare an incorrect, positive response to the A-cue. The opposite pattern is predicted for people with poor CI: longer cue-probe delays should yield lower BX and higher AY accuracy (Barch & Braver, 2009; Stratta, Daneluzzo, Bustini, Prosperini, & Rossi, 2000).

Review of CI Impairment in Schizotypy-Spectrum Psychopathology

CI impairment has been proposed as a heritable vulnerability marker, or endophenotype, of schizophrenia (Barch, Carter, MacDonald, Braver, & Cohen, 2003; Gottesman & Gould, 2003). However, CI must be assessed premorbidly to distinguish risk from factors such as illness outcomes or medication effects. Findings of CI impairment in people with early onset schizophrenia and subclinical schizotypy would support CI as an endophenotype of the disorder. Published patient studies report CI deficits in terms of error patterns, RTs, and d′context comparing schizophrenia groups with healthy and psychiatric control groups (e.g., Barch et al., 2003; Cohen, Barch, Carter, & Servan-Schreiber, 1999; Reilly et al., 2017). For example, patients with schizophrenia show diminished d′context compared with healthy controls on the AX-CPT and DPX (e.g., Barch et al., 2001; Henderson et al., 2012), with increased BX errors in patients, but variable results for other trial types. CI deficits are not unique to schizophrenia, although patients with schizophrenia generally demonstrate impairment that is more severe and stable than other psychiatric groups, such as other psychotic disorders or mood disorders (e.g., Barch et al., 2003; Cohen et al., 1999; Reilly et al., 2017; Richard, Carter, Cohen, & Cho, 2013).

Four studies examined CI in schizotypal personality disorder (SPD) using the AX-CPT or DPX and found greater BX relative to AY errors (Barch et al., 2004; McClure, Barch, Flory, Harvey, & Siever, 2008; McClure et al., 2007, 2010). Only one study has examined CI in clinical high-risk participants, and reported more BX errors and lower d′context than healthy participants (Niendam et al., 2014). There is inconclusive evidence on CI impairment in unaffected relatives: some studies found small to large effects compared with healthy controls, whereas others found no group differences on BX errors or d′context (e.g., Delawalla, Csernansky, & Barch, 2008; López-García et al., 2013; MacDonald, Goghari, et al., 2005; MacDonald et al., 2003; Richard et al., 2013). Only one study examined AX-CPT performance in a subclinical group scoring high on schizotypy questionnaires (Sloat, 2007). Using two-tailed *t* tests, there were no differences in CI compared with healthy controls (our calculations from reported

summary data; authors used one-tailed, focused contrasts to examine differences across multiple groups). In summary, CI deficits occur across the schizotypy spectrum in clinical and some at-risk groups; however, mixed findings were common and there were few studies with unaffected relatives and subclinical schizotypy groups.

Factors That May Influence CI Impairment

Medications and illness duration can impact cognitive ability in schizophrenia. However, CI impairment is not likely attributable to medication effects because deficits are seen in medication-naïve patients (Barch et al., 2001). Indeed, CI impairment occurs in medicated and unmedicated patients compared with controls (e.g., Chung, Mathews, & Barch, 2011; Fornito, Yoon, Zalesky, Bullmore, & Carter, 2011; Lesh et al., 2015; Niendam et al., 2014; Richard et al., 2013; Yoon et al., 2012). Patients with first-episode and chronic schizophrenia show substantial CI deficits on the AX-CPT and DPX compared with controls (e.g., Braver et al., 1999; Cohen et al., 1999; Lesh et al., 2013; Perlstein, Dixit, Carter, Noll, & Cohen, 2003; Stratta et al., 2000). Only one published study directly compared illness episodes: Servan-Schreiber et al. (1996) found that unmedicated, multiepisode patients had lower d′context than unmedicated, first-episode patients. Because research on illness duration is often confounded by medication status, both are important factors to consider when assessing CI.

Associations of Schizotypy Spectrum Symptom Dimensions With CI

Assessing schizotypy as a singular construct can lead to inconsistent, uninterpretable, and invalid findings (Kwapil & Chun, 2015); therefore it is important to examine CI in relation to schizotypy symptom dimensions. Disorganized symptoms have the strongest theoretical and empirical link with CI deficits. Disorganized symptoms are broadly associated with decreased activity in the DLPFC (Goghari, Sponheim, & MacDonald, 2010; Yoon et al., 2008) and with impairment in aspects of executive function (Nieuwenstein, Aleman, & de Haan, 2001). Cohen and colleagues (1999) proposed an association between CI and disorganized symptoms, especially formal thought disorder. There is considerable empirical support for the association of CI deficits and disorganized symptoms, with most studies showing significant associations along the schizotypy spectrum (e.g., Ceccherini-Nelli, Turpin-Crowther, & Crow, 2007; Jones et al., 2010; McClure et al., 2008; Richard et al., 2013; Sloat, 2007).

Cohen and Servan-Schreiber (1992) proposed a link between negative symptoms and CI deficits. Negative symptoms are associated with diminished frontal and prefrontal cortex dopamine-linked activity and executive functioning deficits (e.g., Andreasen, Flaum, Swayze, Tyrrell, & Arndt, 1990; Bora, Yucel, & Pantelis, 2009; Servan-Schreiber et al., 1996). Further, research in patients with schizophrenia indicates hypoactivation of the fronto-parietal network, which is implicated in cognitive control, in relation to task-based negative symptoms (poor reward learning; Culbreth, Gold, Cools, & Barch, 2016). There are theoretical and empirical bases for associations between negative symptoms and executive dysfunction, but compared with disorganized symptoms, there are less explicit theoretical connections between negative symptoms and CI. Associations of CI with negative symptoms have been demonstrated empirically, but less reliably than with disorganized symptoms. Patient studies show mixed results regarding negative symptoms and CI impairment (e.g., Barch et al., 2003; Javitt,

Rabinowicz, Silipo, & Dias, 2007; MacDonald & Carter, 2003; Owoso et al., 2013; Stratta et al., 2000). Further, associations with negative symptoms have not been supported across the schizotypy spectrum: null findings were reported in clinical high-risk, SPD, and subclinical schizotypy groups (McClure et al., 2008; Niendam et al., 2014; Sloat, 2007).

Early phenomenologists described a connection between CI and delusions (Conrad, 1958; Matussek, 1952). Others proposed that hallucinations represent a failure in source monitoring (Bentall, Baker, & Havers, 1991). Stratta and colleagues (2000) expanded upon this idea, suggesting that confusion between internal and external events in hallucinations may be associated with CI impairment given patients' difficulty using the contextual network to determine the source of information. However, these models have not received strong empirical support: most studies using the AX-CPT and DPX found no associations between CI and positive symptoms (e.g., Gold et al., 2012; Javitt et al., 2007; McClure et al., 2008; Owoso et al., 2013). Furthermore, one study reported that associations with positive symptoms were no longer significant after accounting for disorganized symptoms (Becker, 2012).

Limitations of the Literature

The literature on CI in schizophrenia is extensive, but results vary regarding error patterns, magnitude of effects, and association with clinical symptoms. Findings differ even within patient studies, but especially within at-risk studies. Overall, we know little about CI in subclinical schizotypy, particularly from a multidimensional perspective. The use of small samples and heterogeneous variables limits conclusions that can be drawn by qualitative review. Further, the potential for reporting bias, including file drawer effects, and use of the same participants across multiple publications inflates the perceived consistency of findings. Many of these shortcomings could be improved through use of systematic review and meta-analysis. Previous meta-analyses have included CPT tasks to assess factors such as cognitive remediation and executive function-related brain abnormalities (e.g., Grynszpan et al., 2011; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). However, there are no comprehensive meta-analyses of AX-CPT and DPX performance; thus, this is the first known meta-analysis to assess CI deficits across the schizotypy spectrum using these tasks.

Meta-analysis offers advantages over traditional narrative summaries, which may use imprecise search strategies, miss relevant research, gather information improperly, and fail to show overall magnitude of effects (Cooper, 2010; Higgins & Green, 2011). Meta-analysis can overcome random design flaws from primary studies and address reporting biases by obtaining unpublished data and applying corrective techniques. Thus, meta-analysis can determine the validity of synthesized results when drawn from an imperfect literature base.

The goals of this project were to conduct a systematic review of the published and unpublished literature and use meta-analysis to examine CI using AX-CPT and DPX tasks along the schizotypy spectrum compared with healthy and psychiatric control groups, associations between CI and schizotypy symptom dimensions, and the impact of patient and task variables. Some task variables were assessed to examine CI theory (e.g., cue-probe delay should differentially impact groups), whereas other variables were assessed to help researchers select task parameters in future research (e.g., to understand how cue duration or number of trials impacts outcomes).

Method

Planning and a priori decisions were preregistered at Open Science Framework (https://osf.io/qhguz/) before analyses were conducted. Some researchers propose that meta-analysis should represent an atheoretical examination of the available data (Charlton, 1996) whereas others believe hypotheses should be made whenever subgroup analyses are conducted (Sun, Briel, Walter, & Guyatt, 2010). Detailed hypotheses, including effect size predictions, were made but for the sake of space, the reader is referred to Open Science Framework for hypotheses and methodological and analytical decisions.

Literature Search

The following terms were used to search for English and non-English language articles in PsycINFO, PubMed, Google Scholar, and Scopus databases: AX-CPT/DPX/dot pattern expectancy task/CNTRACs/context* integration/context* processing and schizo*/prodromal/high risk/psychosis; context* and ultra high risk. In addition, searches were conducted in the following journals: *Journal of Abnormal Psychology*, *Biological Psychology*, *Biological Psychiatry*, *Schizophrenia Research*, *Schizophrenia Bulletin*, *JAMA Psychiatry*, *Neuropsychology*, *American Journal of Psychiatry*, *Psychological Medicine*, *Journal of Clinical Neuropsychology*, *Psychiatry Research*, *and Schizophrenia Research: Cognition.* References from key papers were examined and 227 researchers in the field were contacted for unpublished data. 42 researchers were contacted to obtain additional information from studies identified for inclusion. Records from 1986 on were systematically screened. Journal and database search was completed in February 2016, and contact of researchers was completed in June 2017.

Inclusion Criteria for Studies and Participants

The following inclusion criteria were defined a priori: (a) inclusion of participants with a diagnostic indicator or psychometric measurement of schizotypy-spectrum psychopathology; (b) use of an AX-CPT or DPX task with at least 10 trials, at least 60% AX trials, and no additional goals/parameters (e.g., ignoring background noise during the task). Studies or participant groups were excluded if data had reported or suspected overlap with another included study or if data were not reported separately for the schizotypy-spectrum group (e.g., studies combined data from participants with schizophrenia and mood disorders with psychotic features). First-degree relative groups were excluded when some participants had psychotic disorders.

The first and second authors coded information. Discrepancies were discussed and resolved between coders. It was planned that the third author would consult in case of remaining disagreements. Researchers often used overlapping samples across articles, did not provide adequate descriptions of samples, or did not respond to communication; thus, unambiguous identification of sample overlap was not always possible. Because inclusion of multiple studies reporting the same data violates assumptions of independence and runs the risk of inflating conclusions, studies were excluded when overlap was suspected or verified.

Analyses

Data analysis followed best practices described by the PRISMA Guidelines (Liberati, Altman, Tetzlaff, et al., 2009; Moher, Liberati, Tetzlaff, Altman, The PRISMA Group, 2009), Cooper (2010), and Higgins and Green (2011). The PRISMA checklist (Moher et al., 2009) is included in the online supplemental material. A random-effects model was selected, which assumes that error may vary systematically across studies. Between-groups effects were converted to Hedges' *g* and within-group effects were converted to Fisher's *z*. Effect sizes from each study were weighted by inverse variance and summarized using Comprehensive Meta-Analysis Version 3 (Borenstein, Hedges, Higgins, & Rothstein, 2015). To estimate variance for each average effect size, 95% confidence intervals are presented in tables. Heterogeneity among effects was analyzed using Q, τ^2, and I^2 (Borenstein, 2009). For subgroup analysis, calculations were run with separate τ^2 estimates for each subgroup. Alpha was set a priori at 0.05.

Between-Group Analyses

Healthy control comparisons. For comparisons between schizotypy-spectrum and healthy control groups, accuracy and d′context are reported across all trial types for short (<3500 ms) and long (>3500 ms) cue-probe delay. See Supplemental Table S1 for reaction time (RT) analyses. To limit the number of analyses, other between-groups analyses only examined key outcomes: AY errors, BX errors, and d′context. For symptom correlations, BX errors and d′context were assessed. Analyses were run separately for each variable to maintain independent data. Schizotypy-spectrum groups were compared with healthy controls for all trial types and d′context at short and long delay.

Psychiatric control comparisons. Patients with schizophrenia were compared with psychiatric controls on AY errors, BX errors, and d′context collapsed across delay conditions. Magnitude of effects between patients with schizophrenia and healthy controls was compared with effects between at-risk participants and healthy controls for AY errors, BX errors and d′context collapsed across delay conditions.

Subgroup analyses. Subgroup analyses compared magnitude of between-groups effects for patients with chronic schizophrenia, first-episode schizophrenia, and at-risk groups versus healthy controls for AY errors, BX errors, and d′context.

Symptom-Task Correlations

Within-group correlations of positive, negative, and disorganized symptoms with d′context and BX errors were synthesized in patients with schizophrenia.

Moderation Analyses

Moderation analyses examined whether AY error, BX error, and d′context effects for schizotypy-spectrum groups compared with healthy controls were affected by categorical measures of cue duration (dichotomized at 500 ms) and cue-probe delay (dichotomized at 3500 ms). Task type was assessed as a moderator of AY errors, BX errors, and d′context; however, because of

unequal distribution across diagnostic groups, task type analyses were only conducted for effects between patients with chronic schizophrenia and healthy controls.

Meta-Regression

Meta-regression assessed prediction of AY error, BX error, and d′context outcomes by continuous variables (Borenstein, 2009). Effects of schizotypy-spectrum groups versus healthy controls were regressed on cue-probe delay and number of trials. Effects of patients with schizophrenia versus healthy controls were regressed on patients' length of illness.

Reporting Biases

Simonsohn's *p*-curve, funnel plots, and the trim-and-fill method assessed asymmetry and skew in distribution of findings as estimations of publication bias and selective reporting. Simonsohn's (2017)*p*-curve application Version 4.052 was used to detect *p*-hacking by plotting significant *p* values and examining the shape of the curve. This technique assumes that significant *p* values are more likely to be small than just under the 0.05 threshold. When the *p*-curve is skewed to the right, evidential value is demonstrated, indicating effects are not solely due to *p*-hacking. Left skew suggests intensive *p*-hacking is likely present (Simonsohn, Nelson, & Simmons, 2014). Separate *p*-curves were plotted for correlations of positive, negative, and disorganized symptoms with BX errors and d′context at short and long delay.

Funnel plots display an inverse graph of effect size on standard error. Ninety-five percent confidence intervals are displayed around the summary effect; when more than 5% of studies fall outside these intervals, it may indicate reporting bias, heterogeneity, or chance (Sterne et al., 2011). Duval and Tweedie's (2000) trim-and-fill method uses symmetry assumptions to estimate the number of "missing" studies, impute those values, and calculate an adjusted effect estimate. This method provides more conservative estimates if plot asymmetry is attributable to reporting bias. Plots were created for effects between schizotypy-spectrum groups and healthy controls, and between schizophrenia and psychiatric comparison groups for AY errors, BX errors, and d′context.

Results

Literature Search

Figure 1 presents a diagram of search results, adapted from the PRISMA Guidelines (Moher et al., 2009). Forty-one independent studies were selected for inclusion in the meta-analyses (see Table 1). Overlapping samples across multiple publications was a major issue: 20 samples were excluded because of confirmed or likely reuse of participants. There was an 82% initial agreement rate between coders for 38 samples that were dual-coded (63% of included studies were dual-coded). Disagreements were resolved by consensus.

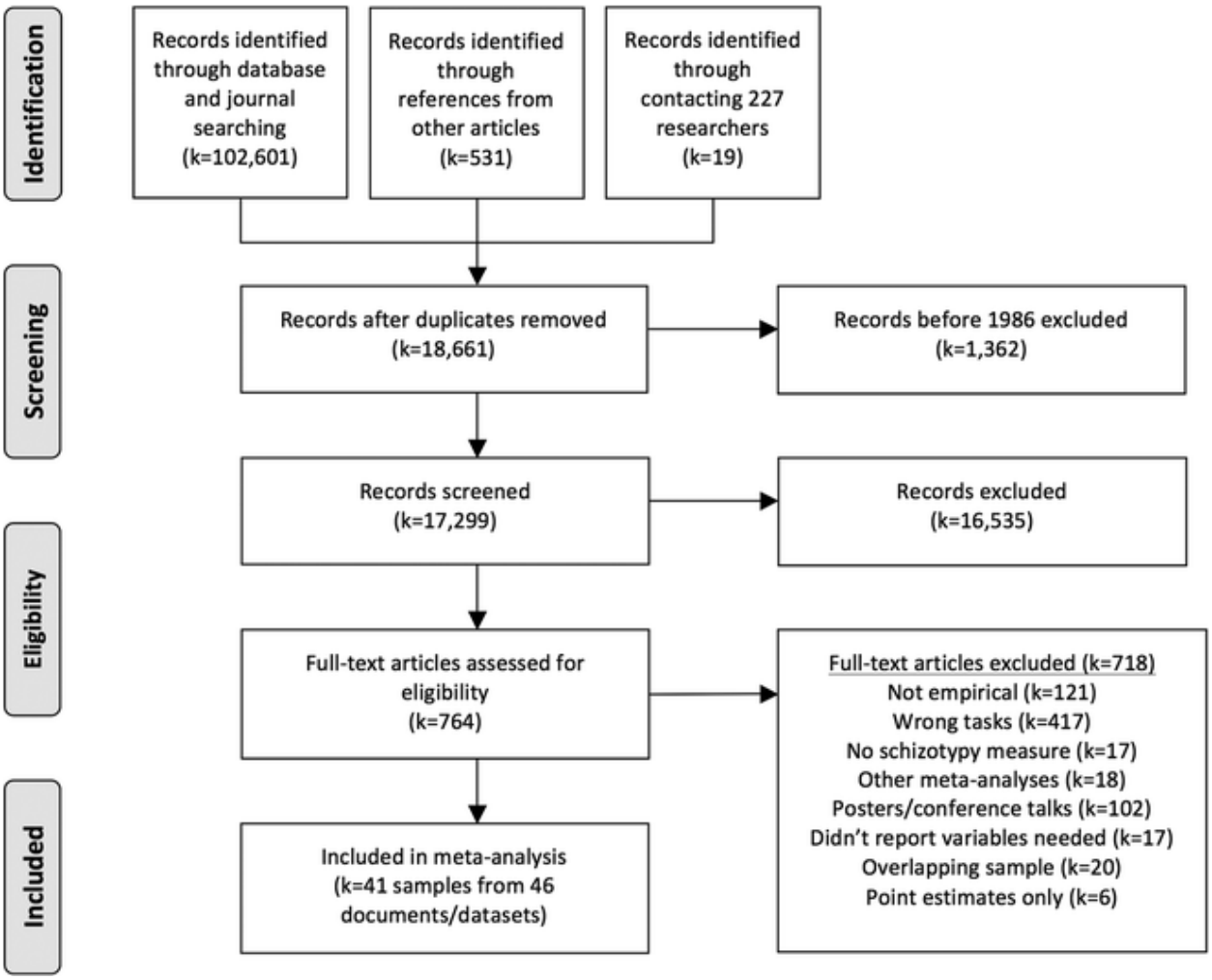

Figure 1. Literature search results. Adapted from "Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement," by D. Moher, A. Liberati, J. Tetzlaff, D. G. Altman, and the PRISMA Group, 2009, PLoS Medicine, 6, p. e1000097. Copyright 2009 by Public Library of Science. Adapted with permission.

Table 1. Sample and Task Information for Studies Included in the Meta-Analysis

Study	Sample	Task
Barch et al. (2001)	14 first-episode schizophrenia 12 healthy control	AX-CPT
Barch, Carter, MacDonald, Braver, and Cohen (2003)	49 first-episode schizophrenia 30 non-schizophrenia psychotic control 72 healthy control	AX-CPT
Barch et al. (2004)	26 SPD 35 healthy control	AX-CPT
Barch, Yodkovik, Sypher-Locke, and Hanewinkel (2008)	57 chronic schizophrenia 37 healthy control	AX-CPT
Becker (2012)	49 chronic schizophrenia 28 healthy control	AX-CPT
Braver, Barch, and Cohen (1999)	16 first-episode schizophrenia 16 healthy control	AX-CPT
Ceccherini-Nelli, Turpin-Crowther, and Crow (2007)	17 chronic schizophrenia 14 non-schizophrenia psychotic control	AX-CPT

Study	Sample	Task
	15 depressed control 16 healthy control	
Chung, Mathews, and Barch (2011)	41 chronic schizophrenia 27 healthy control	AX-CPT
Cohen, Barch, Carter, and Servan-Schreiber (1999)	52 chronic schizophrenia 25 depressed control 31 healthy control	AX-CPT
Delawalla et al. (2006)	27 chronic schizophrenia 31 relatives of schizophrenia 81 healthy control	AX-CPT
Delawalla, Csernansky, and Barch (2008)	30 relatives of schizophrenia 92 healthy control	AX-CPT
Dias, Bickel, Epstein, Sehatpour, and Javitt (2013)	17 chronic schizophrenia 13 healthy control	AX-CPT
Edwards, Barch, and Braver (2010)	22 chronic schizophrenia 14 healthy control	AX-CPT
Fisher (personal communication, 2016)	34 chronic schizophrenia	AX-CPT
Fornito, Yoon, Zalesky, Bullmore, and Carter (2011)	23 first-episode schizophrenia 25 healthy control	AX-CPT
Gold et al. (2012); Henderson et al. (2012)	138 chronic schizophrenia 136 healthy control	DPX
Holmes et al. (2005)	7 chronic schizophrenia 10 depressed control 9 healthy control	AX-CPT
Jones, Sponheim, and Macdonald (2010)	47 chronic schizophrenia 48 healthy control	DPX
Lesh et al. (2015)	23 first-episode, medicated schizophrenia 22 first-episode, unmedicated schizophrenia 37 healthy control	AX-CPT
López-García et al. (2016)	15 chronic schizophrenia-spectrum 16 relatives of schizophrenia 20 healthy control	DPX
López-García, Young, Marín, Molero, and Ortuño (2015)	40 chronic schizophrenia-spectrum 26 relatives of schizophrenia 63 healthy control	DPX
MacDonald (2002)	AX-CPT: 24 chronic schizophrenia, 24 relatives of schizophrenia, 29 healthy control DPX: 17 chronic schizophrenia, 16 relatives of schizophrenia, 28 healthy control	AX-CPT, DPX
MacDonald and Carter (2003)	17 chronic schizophrenia 17 healthy control	AX-CPT
McClure, Barch, Flory, Harvey, and Siever (2008)	63 SPD 25 non-Cluster A personality disorder 42 healthy control	AX-CPT
Merrill et al. (2017)	43 chronic schizophrenia 19 healthy control	AX-CPT
Paavola (2013)	47 relatives of schizophrenia 57 healthy control	DPX
Perlstein, Dixit, Carter, Noll, and Cohen (2003)	16 chronic schizophrenia 15 healthy control	AX-CPT
Poppe, Carter, Minzenberg, and MacDonald (2015)	19 chronic schizophrenia 33 relatives of schizophrenia 50 healthy control	AX-CPT

Study	Sample	Task
Poppe et al. (2016)	47 chronic schizophrenia 56 healthy control	DPX
Reilly et al. (2017)	402 chronic schizophrenia 304 bipolar with psychotic features 210 healthy control	DPX
Richard, Carter, Cohen, and Cho (2013)	63 first-episode schizophrenia 31 relatives of schizophrenia 83 healthy control 47 non-schizophrenia psychotic control	AX-CPT
Sheffield et al. (2014)	104 chronic schizophrenia 132 healthy control	AX-CPT, DPX
Sheffield et al. (2015)	46 chronic schizophrenia 54 healthy control	DPX
Sloat (2007)	25 psychometric schizotypy 18 psychometric vulnerable to depression 38 healthy control	AX-CPT
Stratta, Daneluzzo, Bustini, Prosperini, and Rossi (2000)	20 chronic schizophrenia 20 healthy control	AX-CPT
Thoma and Daum (2008)	23 chronic schizophrenia 22 depressed control 20 healthy control	AX-CPT
Thoma, Zoppelt, Wiebel, and Daum (2007)	26 chronic schizophrenia 13 healthy control	AX-CPT
Todd et al. (2014)	33 chronic schizophrenia 58 healthy control	AX-CPT
Woodward (personal communication, 2016)	15 first-episode schizophrenia 35 chronic schizophrenia 19 bipolar with psychotic features 39 healthy control	AX-CPT
Yoon et al. (2012)	51 first-episode schizophrenia 51 healthy control	AX-CPT
Zhang et al. (2015)	339 chronic schizophrenia 665 healthy control	DPX

Table 2 presents demographic information. Schizotypy-spectrum groups included patients with chronic and first-episode schizophrenia, people with SPD, unaffected relatives, and people with psychometrically identified schizotypy. Psychiatric comparison groups included people with nonschizophrenia psychosis, nonpsychotic depression, bipolar disorder, non-Cluster A personality disorders, and psychometrically identified risk for depression. As previously described, trial types included AX trials (context-processing and preparatory), BX trials (context-processing), AY trials (preparatory), and BY trials (general cognition and attention; MacDonald, Goghari, et al., 2005).

Between-Group Analyses

Healthy control comparisons. Schizotypy-spectrum groups performed worse than healthy controls on almost every outcome (see Table 3). They made significantly more errors across all trial types for short delays, and across AX, BX, and BY trials for long delays. Schizotypy-spectrum groups had significantly lower d′context for short and long delays. Very small (long delay) to small (short delay) effects were found for AY and BY errors. Medium effects were found for d′context (short delay) and AX and BX errors (short and long delay). A large effect

was found for d′context at long delay. Significant heterogeneity was found across studies for all outcomes except short delay BX errors.

Confidence intervals around effects were indirectly compared to infer differences across trial types. Indirect comparisons are observational and should be interpreted cautiously. For short delay, confidence intervals around AX errors overlapped slightly with those for AY and BY errors; confidence intervals for BX errors showed no overlap with AY and BY errors. For long delay, neither AX nor BX errors' confidence intervals overlapped with those for AY and BY errors, suggesting that effects for CI-critical trials were larger than effects for trials tapping preparatory or general abilities. Overall, schizotypy-spectrum groups generally performed worse and error patterns were consistent with a specific deficit in CI.

Psychiatric control comparisons. Patients with schizophrenia were compared with psychiatric controls. Table 4 presents AY error, BX error, and d′context results. Figure 2 presents a forest plot of d′context effects. The schizophrenia group had significantly lower d′context than the psychiatric control group at the level of a medium effect, with significant heterogeneity across studies. Patients with schizophrenia made significantly more BX errors than other psychiatric patients at the level of a small effect. Finally, there was no group difference in AY errors (very small effect). Heterogeneity across studies was not significant for AY and BX errors. In sum, CI was more impaired in schizophrenia than other psychiatric groups.

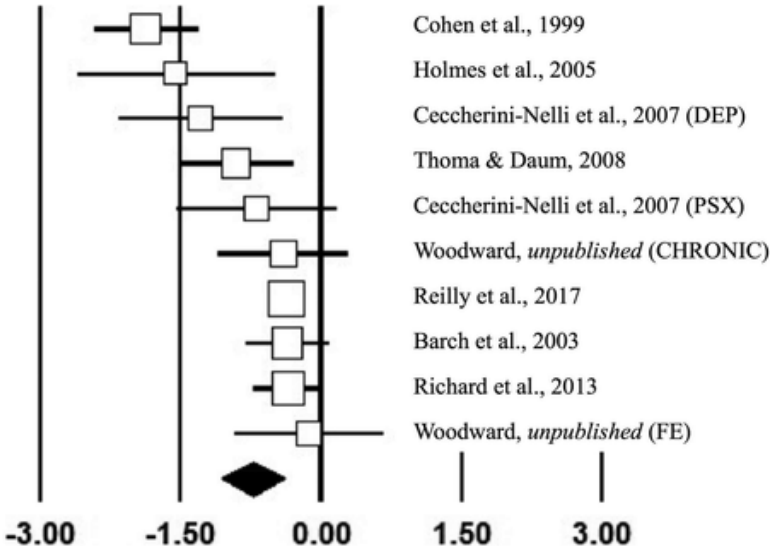

Figure 2. Forest plot of d′context effects for schizophrenia versus psychiatric comparison groups. DEP = depressed controls; PSX = psychotic controls; FE = first-episode schizophrenia. The center of each white box represents Hedges' g for single studies, the size of the box represents relative weight (inverse variance), and the bars represent 95% confidence intervals. Negative effects indicate the schizophrenia group performed worse than the psychiatric comparison group. The black diamond represents estimated Hedges' g for the overall effect, with the width showing 95% confidence intervals.

Table 2. Summary Demographic Information

Variable	First-episode, unmedicated	First-episode, medicated	Chronic schizophrenia	At-risk group	Healthy controls	Psychiatric controls
Age: *M* (*SD*)	23.70 (1.49) *k* = 5, *n* = 164	20.37 (.59) *k* = 4, *n* = 12	34.56 (4.89) *k* = 28, *n* = 2018	33.97 (9.60) *k* = 11, *n* = 364	30.47 (6.63) *k* = 40, *n* = 2659	33.37 (6.47) *k* = 12, *n* = 447
Education (years): *M* (*SD*)	12.65 (.44) *k* = 5, *n* = 164	12.47 (.35) *k* = 4, *n* = 112	11.78 (1.71) *k* = 22, *n* = 1475	13.52 (1.17) *k* = 9, *n* = 323	12.93 (2.67) *k* = 33, *n* = 2186	13.76 (1.30) *k* = 7, *n* = 156
Length of illness (years): *M* (*SD*)	.58 *k* = 1, *n* = 22	.59 (.21) *k* = 2, *n* = 38	7.92 (4.27) *k* = 11, *n* = 849			
Female	30.07% *k* = 5, *n* = 164	26.84% *k* = 4, *n* = 112	35.81% *k* = 30, *n* = 2096	50.75% *k* = 11, *n* = 364	49.16% *k* = 39, *n* = 2639	53.97% *k* = 12, *n* = 447
White		0% *k* = 1, *n* = 15	59.88% *k* = 11, *n* = 532	54.31% *k* = 6, *n* = 202	60.67% *k* = 15, *n* = 1181	69.86% *k* = 3, *n* = 259
Black		80.00% *k* = 1, *n* = 15	43.22% *k* = 7, *n* = 783	43.42% *k* = 3, *n* = 108	27.98% *k* = 7, *n* = 527	21.15% *k* = 4, *n* = 284
Latino		0% *k* = 1, *n* = 15	29.40% *k* = 4, *n* = 228	34.92% *k* = 4, *n* = 126	53.77% *k* = 4, *n* = 160	2.70% *k* = 2, *n* = 37
Asian			50.75% *k* = 4, *n* = 1180	8.33% *k* = 3, *n* = 108	69.70% *k* = 3, *n* = 1066	3.3% *k* = 2, *n* = 240
Other race/ethnicity		20.00% *k* = 1, *n* = 15	7.22% *k* = 3, *n* = 611	2.60% *k* = 2, *n* = 84	7.10% *k* = 3, *n* = 385	4.23% *k* = 3, *n* = 259
% Medicated	0% *k* = 5, *n* = 164	78.22% *k* = 3, *n* = 61	99.71% *k* = 16, *n* = 1044			

Note. *k* = number of samples. *n* = number of participants. For categorical variables, numbers represent percentage within the subset of samples providing data for that category.

Table 3. Schizotypy-Spectrum Versus Healthy Control Groups for Short and Long Cue-Probe Delay

Measure	*k*	Hedges' *g*	Lower CI	Upper CI	*p* value	*Q*	*df*(*Q*)	*p* value	I^2	τ^2
Short AX errors	21	**.59**	0.41	0.77	$1.22E^{-10}$	51.59	20	$1.31E^{-4}$	61.23	.095
Short AY errors	22	.33	0.19	0.46	$1.94E^{-6}$	33.59	21	.040	37.48	.036
Short BX errors	22	**.61**	0.50	0.71	.00	22.22	21	.39	5.49	.0035
Short BY errors	20	.32	0.14	0.50	$6.48E^{-4}$	51.73	19	$7.26E^{-5}$	63.27	0.99
Short d'context	24	***–.84***	–1.06	–0.63	$1.64E^{-14}$	96.00	23	$6.84E^{-11}$	76.04	.20
Long AX errors	25	.55	0.42	0.68	.00	38.35	24	.032	37.43	.033
Long AY errors	26	.00	–0.17	0.18	.97	82.07	25	$5.38E^{-8}$	69.54	.12
Long BX errors	28	**.59**	0.47	0.72	.00	44.53	27	.018	39.36	.037
Long BY errors	25	.19	–0.01	0.39	.06	100.39	24	$2.57E^{-11}$	76.09	.17
Long d'context	28	**–.76**	–0.91	–0.61	.00	67.11	27	$2.87E^{-5}$	59.77	.08

Note. *k* = number of samples; Hedges' *g*: medium effects in bold, large effects in bold italics.

Table 4. Schizophrenia Versus Psychiatric Comparison Groups

Measure	*k*	Hedges' *g*	Lower CI	Upper CI	*p* value	*Q*	*df*(*Q*)	*p* value	I^2	τ^2
AY errors	6	.02	–0.12	0.15	.81	1.95	5	.86	.00	.00
BX errors	8	.33	0.19	0.46	$1.65E^{-6}$	3.30	7	.86	.00	.00
d'context	10	**–.73**	–1.07	–0.40	$1.73E^{-5}$	36.38	9	$3.39E^{-5}$	75.26	.19

Note. *k* = number of samples; Hedges' *g*: medium effects in bold.

Subgroup analyses. Planned subgroup analyses were run dividing the schizotypy-spectrum group into individuals with schizophrenia and those at risk. Table 5 presents results and Figure 3 presents a forest plot of d′context effects. The schizophrenia group had significantly lower d′context than healthy controls (large effect), more BX errors (medium effect), and more AY errors (small effect). Significant heterogeneity was observed across studies for all effects in the schizophrenia group. Compared with healthy controls, the at-risk group had significantly lower d′context and more BX errors (small effects). There were no group differences for AY errors (very small effect). Heterogeneity across studies was not significant in the at-risk group.

Table 5. Diagnostic Subgroup Analyses

Measure	Subgroup	*k*	Hedges' *g*	Lower CI	Upper CI	*Q*	*df*(*Q*)	*p* value
AY errors	Schizophrenia	29	.29	0.16	0.42			$1.79E^{-1}$
	At-risk	8	–.04	–0.24	0.15			.66
	Difference between subgroups					7.82	1	.0052
BX errors	Schizophrenia	32	**.71**	0.61	0.80			.0000
	At-risk	9	.36	0.15	0.58			.0011
	Difference between subgroups					8.14	1	.0043
d'context	Schizophrenia	28	***–.94***	–1.08	–0.80			.0000
	At-risk	9	–.40	–0.56	–0.23			$3.70E^{-6}$
	Difference between subgroups					23.45	1	$1.30E^{-6}$

Note. *k* = number of samples; Hedges' *g*: medium effects in bold, large effects in bold italics. Difference between subgroups involve indirect comparisons and should be interpreted cautiously.

Indirect comparisons indicated that relative to healthy controls, the schizophrenia group had stronger effects than the at-risk group for AY errors, BX errors, and d′context. Significant unexplained variance remained after accounting for diagnostic status. Individuals with schizophrenia and those at risk showed CI deficits, and indirect comparisons suggested more pronounced deficits in patients.

Planned comparisons examined patients with chronic schizophrenia (>1.5 years of illness), first-episode schizophrenia (≤1.5 years of illness), and at-risk groups. Indirect comparisons indicated no difference in effect size between chronic and first-episode groups compared with controls (Supplemental Table S2). Length of illness was not associated with CI when examined categorically.

Symptom-Task Correlations

Correlations between symptom dimensions and task outcomes were examined in patients with schizophrenia (see Table 6). Disorganized symptoms showed significant associations with d′context and BX errors (small effects), with significant heterogeneity across studies. Negative symptoms were significantly correlated with d′context and BX errors (small effects). Positive symptoms were not associated with CI (very small effects). No significant heterogeneity across studies was observed for positive or negative symptom correlations. Indirect comparisons suggested that magnitude of effects did not differ among the three symptom dimensions.

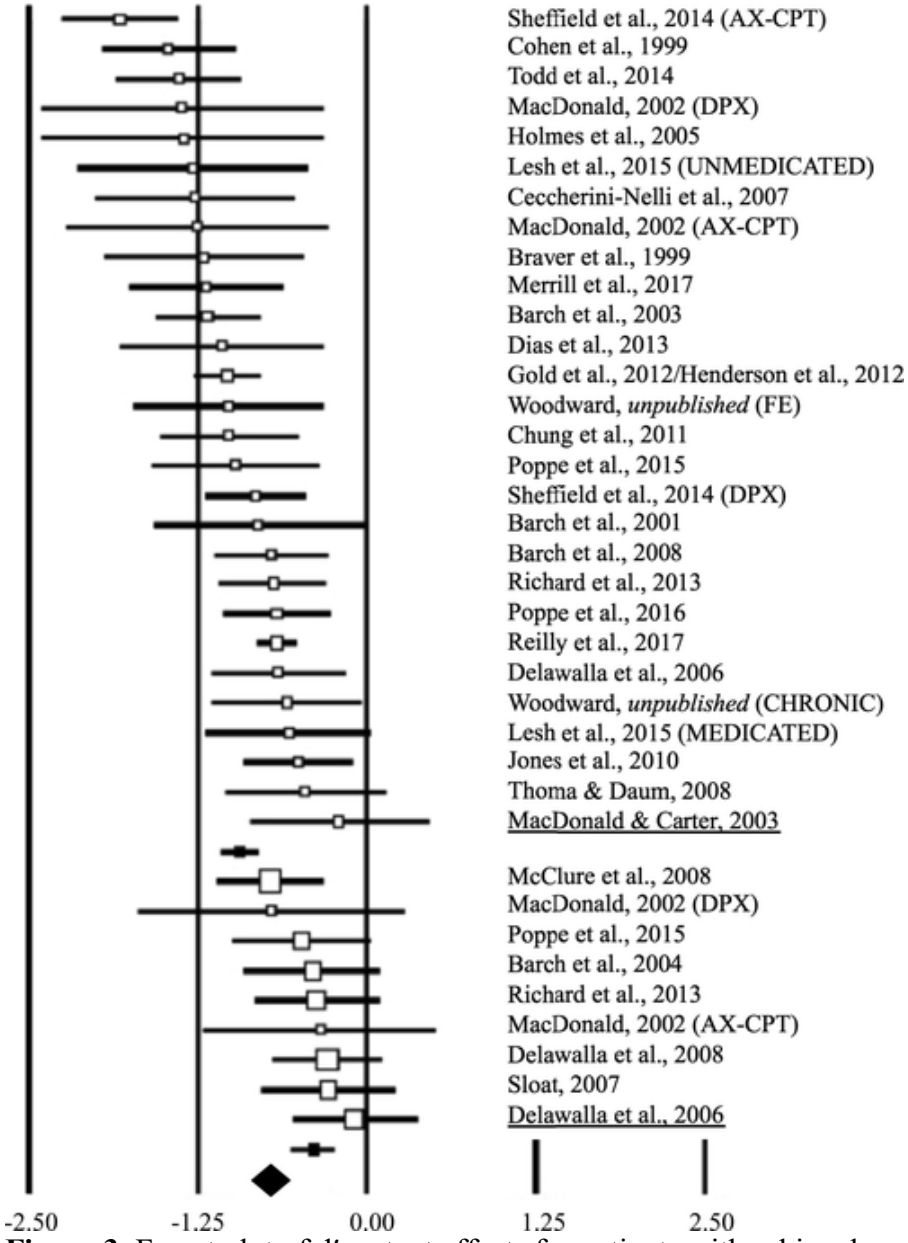

Figure 3. Forest plot of d′context effects for patients with schizophrenia and at-risk group versus healthy controls. FE = first-episode schizophrenia. Effects for schizophrenia on top and at-risk group on bottom. The center of each white box represents Hedges' g for single studies, the size of the box represents relative weight (inverse variance), and the bars represent 95% confidence intervals. Negative effects indicate the schizotypy-spectrum group performed worse than the control group. Black squares represent estimated Hedges' g for the overall subgroup effect, with the bars showing 95% confidence intervals. The black diamond represents the overall effect across subgroups, with the width showing 95% confidence intervals.

Table 6. Symptom-Task Correlations in Schizophrenia Patients

Symptoms	Variable	*k*	Pearson's *r*	Lower CI	Upper CI	*p* value	*Q*	*df*(*Q*)	*p* value	I^2	τ^2
Positive	d'content	17	–.054	–0.12	0.012	.11	17.35	16	.36	7.77	.0015
	BX errors	12	.049	–0.021	0.12	.17	10.98	11	.45	.00	.0000
Negative	d'content	17	–.15	–0.22	–0.069	.00	20.80	16	.19	23.07	.0055
	BX errors	12	.12	0.017	0.21	.021	14.64	11	.20	24.87	.0068
Disorganized	d'content	14	–.22	–0.34	–0.094	.001	28.65	13	.0073	54.63	.029
	BX errors	10	.24	0.070	0.39	.006	19.13	9	.024	52.96	.037

Moderation Analyses

Cue duration and cue-probe delay were assessed as categorical moderators of outcomes between schizotypy-spectrum and healthy control groups (Supplemental Tables S3 and S4). Cue duration and cue-probe delay moderated AY accuracy: long cues (≥1,000 ms) showed significantly stronger effects than short cues (<1,000 ms), and short delays (<3500 ms) showed significantly stronger effects than long delays (≥3500 ms). Neither cue duration nor cue-probe delay moderated effects for BX errors or d′context.

Task type (AX-CPT vs. DPX) was assessed as a categorical moderator of outcomes between patients with chronic schizophrenia and healthy controls; there were insufficient DPX studies for analysis with other groups. Task type did not moderate effects for AY errors, BX errors, or d′context. Overall, schizotypy-spectrum CI deficits are robust across task parameters.

Meta-Regression

Number of trials and cue-probe delay were assessed as continuous predictors of outcomes between schizotypy-spectrum and healthy control groups. Figure 4 depicts number of trials regressed on d′context. Number of trials explained significant variance in d′context and AY errors: with more trials, studies showed weaker positive AY effects and stronger negative d′context effects (Supplemental Table S5). Number of trials did not predict BX error effects. Neither cue-probe delay nor patients' length of illness predicted AY error, BX error, or d′context effects.

Reporting Biases

Funnel plots and the trim-and-fill method were employed for short and long delay AY errors, BX errors, and d′context in schizotypy-spectrum versus healthy control groups; AY errors, BX errors, and d′context scores collapsed across delay in schizophrenia versus psychiatric control groups; and correlations of positive, negative, and disorganized symptoms with short and long delay BX errors and d′context in schizophrenia. Zero to nine values were imputed per plot and none of the adjusted estimates differed significantly from observed estimates. *p*-curves were created for correlations of positive, negative, and disorganized symptoms with BX errors and d′context at short and long delay. None of the curves were significant for *p*-hacking. *p*-curves for disorganized and negative symptom correlations with d′context demonstrated evidential value. Other curves could not be generated or were inconclusive.

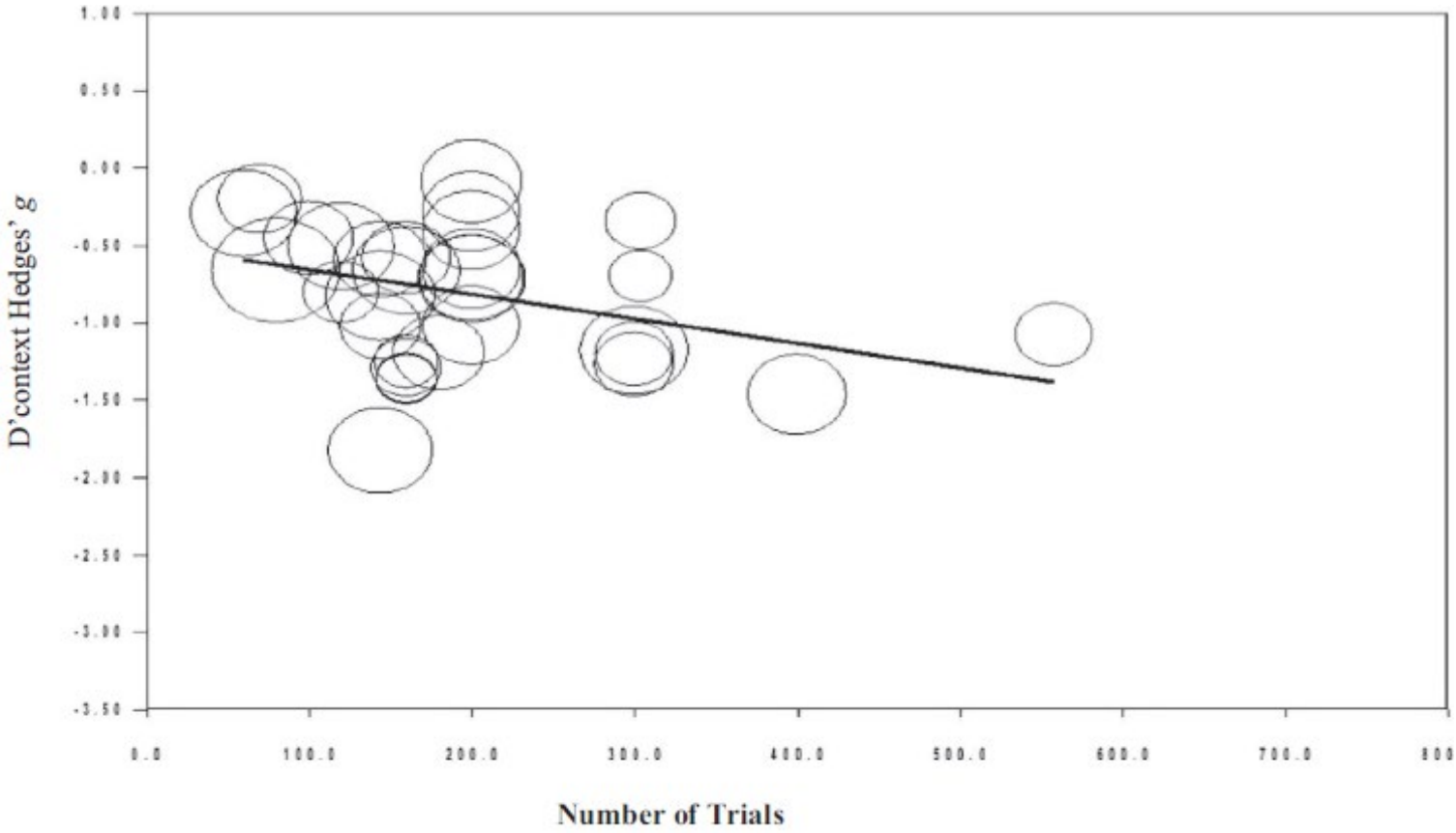

Figure 4. Meta-regression of number of trials predicting Hedges' g for d′context in schizotypy-spectrum versus healthy control groups. Circles represent individual studies, with the size showing relative weight (inverse variance).

Discussion

Impaired CI has been proposed as a specific deficit in schizophrenia that presents before psychosis onset and may be implicated in the development of certain schizotypic symptoms. Numerous studies have used AX-CPT and DPX tasks to assess CI in patients with schizophrenia, but few have examined CI in nonpsychotic schizotypy. The literature is limited by use of small samples, varying task parameters, and heterogeneous patient characteristics that complicate interpretation of findings. Meta-analysis is particularly suitable for mitigating many of these limitations. The current study was the first comprehensive meta-analysis of CI impairment and the impact of relevant variables using the AX-CPT and DPX in the schizotypy-spectrum. The study expands upon the extant literature by including a comprehensive synthesis of published and unpublished data using these tasks, presenting conclusions from independent data, providing estimates of effect sizes across a large number of studies, and examining reporting biases.

Summary of Findings

Forty-one independent samples were included in the meta-analyses. Results supported CI impairment across the schizotypy spectrum, as measured by AX-CPT and DPX tasks. Deficits in patients with schizophrenia were substantial and stable across illness duration. At-risk groups

showed milder CI disruption when indirectly compared with schizophrenia groups. Disorganized and negative symptoms were inversely correlated with CI, whereas positive symptoms were unassociated. Larger effects were found with more trials, but no other task parameters appreciably affected outcomes. Results did not differ using corrective methods to adjust effect estimates. Further, *p*-curve analyses showed no evidence that symptom correlations were solely attributable to *p*-hacking. Although reporting biases can never be ruled out, they did not grossly impact findings, supporting validity of the current results.

Interpretation of Results

Schizotypy-spectrum groups performed worse than healthy controls on most outcomes. However, schizotypy-spectrum errors on AX and BX trials were substantial and surpassed BY errors. AX and BX trials are thought to tap CI and BY trials roughly estimate generalized impairment (MacDonald, Goghari, et al., 2005). Thus, these differential effect sizes are consistent with a specific deficit in CI that extends beyond generalized deficits because of issues such as inattention and amotivation (Chapman & Chapman, 1973; MacDonald & Carter, 2002).

Negligible to small effects were found for AY accuracy: schizotypy-spectrum groups made slightly more errors than healthy controls. AY errors are proposed to reflect intact CI because goal maintenance should create a positive response expectancy for A cues (Barch & Braver, 2009; Henderson et al., 2012). However, MacDonald, Goghari, et al. (2005) suggested that elevated AY errors in schizophrenia may reflect poor response inhibition. A crossover effect—in which schizotypy-spectrum groups perform worse than controls on BX trials but better on AY trials—is theoretically compelling but has not received strong empirical support. Thus, it seems more likely that the BX-AY discrepancy constitutes a relative difference within schizotypy rather than an absolute difference between groups (e.g., Barch et al., 2004; Henderson et al., 2012).

Consistent with CI theory (Cohen et al., 1999; MacDonald, Carter, et al., 2005), the current results indicated that CI deficits were more pronounced in patients with schizophrenia than other psychiatric groups, including non-schizophrenia psychosis. This indicates that CI may be specifically disrupted in schizophrenia beyond general psychiatric impairment. Indirect comparisons should be interpreted cautiously but suggest that individuals with schizophrenia likely have greater impairment than those at risk. In terms of unstandardized errors, patient and at-risk groups made about 4% more BX errors than healthy controls. People who have never experienced psychosis—and most likely never will—still show significant cognitive impairment. This supports theories that CI may be a precursor to schizophrenia, or even a mechanism influencing its development (Barch & Braver, 2009).

Subgroup analyses revealed similar effects for chronic and first-episode patients, with both showing large CI deficits compared with healthy participants. These results were supported by meta-regression findings that illness duration did not predict outcomes. This is partially consistent with findings from a longitudinal study indicating that CI performance in first-episode patients was comparable between baseline and 1-year follow-up for short delay, but improved for long delay (Richard et al., 2013). Current results suggest that CI deficits may be stable throughout illness, although additional longitudinal studies are warranted. Given that CI is present premorbidly and at psychosis onset, persists throughout illness, and is not episode-

limited, it may be a stable vulnerability indicator for schizophrenia (Barch et al., 2003; Nuechterlein et al., 1992).

Chan and Gottesman (2008) proposed requirements for endophenotypic markers. Based on research to date, CI fulfills five of six criteria: CI deficits are associated with illness, state-independent, present in unaffected family members, reliably measured, and show diagnostic specificity. Previous research indicated that DPX performance is influenced by the Val158Met COMT polymorphism, a gene associated with risk for schizophrenia (López-García, Young, Marín, Molero, & Ortuño, 2015; MacDonald, Carter, Flory, Ferrell, & Manuck, 2007). However, it is unclear whether CI impairment is more prevalent among affected versus unaffected relatives of schizophrenia probands. Investigating this final criterion is an important step if CI is to be established as an endophenotype, which would allow researchers to quickly and nonintrusively screen people purportedly at risk for schizophrenia. This could aid in identifying individuals for prophylactic intervention and investigating risk and protective variables implicated in the development of schizotypy-spectrum disorders.

CI and schizotypy symptoms. Within schizophrenia groups, disorganized and negative symptoms were associated with impaired CI, whereas positive symptoms were not. The small effect sizes may, in part, reflect that assessment of CI across symptom dimensions was not a primary goal of most studies. The literature includes many correlations run in mixed symptom groups with varied representation and severity of each symptom dimension, using conceptualizations driven largely by measures rather than theory. We propose that future studies should be designed to assess symptom associations with CI in adequately powered samples, beginning with strong theoretical conceptualizations of dimensions, valid operationalization and measurement of symptoms, and recruitment of schizophrenia-spectrum groups with comparable representation of each symptom dimension.

Despite the shortcomings of the literature, current findings indicate robust associations of disorganized and negative symptoms with CI. These differential associations are consistent with theories connecting neurocognitive impairment with disorganized and negative symptoms (Barch et al., 2001; Cohen et al., 1999; Goghari et al., 2010; Yoon et al., 2008). Neuroimaging studies have supported the association between CI and disorganized symptoms. For example, MacDonald, Carter, et al. (2005) showed that diminished prefrontal activity following B-cues was associated with greater BX errors in patients with schizophrenia and greater disorganized symptoms. Yoon et al. (2008) found that disorganized symptoms were related to decreased DLPFC activity and diminished connectivity to a broader neural network implicated in cognitive control. Poor top-down control may contribute to impaired CI and behavioral symptoms of disorganization (MacDonald, Carter, et al., 2005; Yoon et al., 2008).

Early phenomenologists proposed connections between positive symptoms and disintegration of perception from the environmental context (Conrad, 1958; Matussek, 1952). This was not supported by the present meta-analysis: positive symptoms showed negligible associations with CI. There are gaps in understanding the integration of "context" across different levels of processing. It remains an empirical question whether performance on neurocognitive tasks would translate to behavioral manifestations of poorly integrated context described in the phenomenological literature.

Moderating factors. Task type, cue duration, and cue-probe delay did not moderate effects between schizotypy-spectrum and healthy control groups for BX errors or d′context. The null delay findings are surprising given theories that CI performance should deteriorate more for schizotypy-spectrum groups than controls across longer delay periods (Barch & Braver, 2009). Results may suggest that performance deficits attributable to poor maintenance of context do not reliably manifest above and beyond those attributable to initial poor representation of context. However, it is possible that context maintenance effects would be revealed using longer delay periods. Authors aiming to distinguish representation and maintenance of context may consider cue-probe delays greater than 10 seconds, the maximum duration in the included studies.

Because novel dot patterns in the DPX make cue maintenance more challenging than in the AX-CPT (Barch et al., 2009), the DPX may be more sensitive to subtle deficits in at-risk individuals by avoiding possible ceiling effects. Although task type did not affect outcomes, analyses did not assess this in at-risk groups. Task type could only be examined as a moderator for outcomes between schizophrenia and healthy control groups because the DPX was used infrequently. Further study is needed to examine whether the DPX is a more appropriate measure of CI in less impaired individuals. Number of trials predicted group differences with more trials yielding stronger d′context effects, likely due to improved reliability. Overall, CI deficits were robust across task parameters.

Limitations and Recommendations

The current study reflects limitations in the literature, especially inability to examine medication effects. Too few studies (k = 3) examined medicated, first-episode patients to provide adequate power for subgroup analysis. Most patients with chronic schizophrenia in the literature were medicated and in nonacute phases of illness. Further research is needed to examine the impact of medication and distinguish illness duration from medication status. Few studies have tackled these issues. Using a cross-sectional design, Lesh et al. (2015) found that unmedicated first-episode patients had worse CI than medicated first-episode patients at the level of a medium effect. In preliminary cross-sectional results from Woodward (personal communication, 2016; Giraldo-Chica, Rogers, Damon, Landman, & Woodward, 2018), medicated first-episode patients (n = 15) had worse CI than medicated chronic patients (n = 35) at the level of a small effect. Finally, Barch and colleagues' (2003) longitudinal design showed that first-episode patients had comparable CI performance when medication-naïve and following antipsychotic treatment four weeks later. Overall, it remains unclear how medications and illness progression impact CI. Research directly comparing medicated and unmedicated chronic patients with medicated and unmedicated first-episode patients could help clarify these relationships. Additionally, it could be helpful to differentiate among patients who are medication-naïve, medication noncompliant, and so forth

Cognitive impairment often predicts functional outcome in schizophrenia, thus it would be beneficial to understand how CI deficits influence functioning and quality of life in social and occupational settings. These relationships could not be assessed in this meta-analysis because too few studies reported associations with functional outcome. Those that did generally found correlations of CI with global and community functioning, and performance-based skills in

patients with schizophrenia, with effects ranging from negligible to large (Gold et al., 2012; Richard et al., 2013; Sheffield et al., 2014; Stratta et al., 2000; Todd et al., 2014). Given their applicability to intervention, further assessment of CI and functional outcome is warranted.

Inclusion of participants in multiple publications was widespread, and overlap in samples was not always clearly described. There were instances in which CI data for more than half the sample were previously published. Ethical issues aside, this practice is problematic because it inflates perceived reliability of findings in qualitative reviews and hinders data synthesis in quantitative reviews. If researchers reuse data across publications, it is recommended that they acknowledge this and provide subset analyses with new participants to distinguish which data are novel.

There was significant heterogeneity across studies in many of the current meta-analyses. The diagnostic and parametric variables used to predict CI outcomes did not fully account for variability in performance, suggesting that there is still much to learn about what impacts CI. We proposed some variables that may contribute to heterogeneity, such as unexamined medication effects and poorly measured variation in symptoms, but we cannot rule out that other confounding factors influenced results (e.g., educational background, socioeconomic status).

Finally, the term CI has been used extensively in the clinical literature and there are numerous neurocognitive tasks that assess similar constructs. The current meta-analysis took a focused approach by including two tasks that were determined to best capture CI as defined in this paper; however, it is unclear whether conclusions about CI impairment as measured by AX-CPT and DPX would generalize to other measures purportedly assessing "CI."

Summary and Conclusions

CI impairments measured with AX-CPT and DPX tasks appear to be present across the schizotypy spectrum and occur in premorbid, active, and residual phases of schizophrenia. Thus, CI is not simply an episode marker or consequence of the catastrophic effects of schizophrenia. CI is associated with disorganized and negative symptoms of schizophrenia and appears stable throughout the course of illness. Current results support theories that CI may be a stable vulnerability factor for schizophrenia. Further study is warranted to confirm whether CI is an endophenotype, clarify its role in schizotypy-spectrum symptoms and impairment, and determine whether deficits can be remediated. Recommendations for future research include focus on longitudinal studies, at-risk samples, research designed to differentiate effects of medication and duration of illness or number of illness episodes, research designed to assess associations of symptom dimensions with CI, and examination of the relationship between CI and functioning.

The implication of CI in the development and expression of schizotypy-spectrum psychopathology has roots in phenomenological, neural, and cognitive neuroscience theories. Foundational research in this area has established a strong basis for CI impairment that is linked to cognitive and neurological outcomes. Important next steps include developing a nuanced understanding of how specific factors may interact to influence CI in schizotypy and integrating this research across fields of study for a more holistic understanding of the mechanisms at play.

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