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Both Unmedicated and Medicated Individuals with Schizophrenia Show Impairments Across a Wide Array of Cognitive and Reinforcement Learning Tasks

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Abstract

Background: Schizophrenia is a disorder characterized by pervasive deficits in cognitive functioning. However, few well-powered studies have examined the degree to which cognitive performance is impaired even among individuals with schizophrenia not currently on antipsychotic medications using a wide-range of cognitive and reinforcement learning measures derived from cognitive neuroscience. Such research is particularly needed in the domain of reinforcement learning, given the central role of dopamine in reinforcement learning, and the potential impact of antipsychotic medications on dopamine function.

Methods: The present study sought to fill this gap by examining healthy controls (N=75), unmedicated (N=48) and medicated (N=148) individuals with schizophrenia. Participants were recruited across 5 sites as part of the CNTRaCS Consortium to complete tasks assessing processing speed, cognitive control, working memory, verbal learning, relational encoding and retrieval, visual integration, and reinforcement learning.

Results: Individuals with schizophrenia who were not taking antipsychotic medications, as well as those taking antipsychotic medications, showed pervasive deficits across cognitive domains

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including reinforcement learning, processing speed, cognitive control, working memory, verbal learning, and relational encoding and retrieval. Further, we found that chlorpromazine equivalency rates were significantly related to processing speed and working memory, while there were no significant relationships between anticholinergic load and performance on other tasks.

Conclusions: These findings add to a body of literature suggesting that cognitive deficits are an enduring aspect of schizophrenia, present in those off antipsychotic medications as well as those taking antipsychotic medications.

Impairments in cognitive functioning are a core feature of schizophrenia with deficits seen throughout the course of illness including at the first episode (Barch et al., 2001; Bilder et al., 2000; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009; Saykin et al., 1994) and in adults with chronic schizophrenia (Barch & Ceaser, 2012; Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005; Green, Kern, Braff, & Mintz, 2000; Nuechterlein et al., 2004). Impairments are consistently reported in a broad range of cognitive domains including processing speed, verbal learning, working memory, cognitive control, visual integration and reinforcement learning (Butler, Silverstein, & Dakin, 2008; Dickinson, Ramsey, & Gold, 2007; Gold et al., 2012; Lee & Park, 2005; Lesh, Niendam, Minzenberg, & Carter, 2011; Macdonald & Carter, 2003; Minzenberg, Laird, Thelen, Carter, & Glahn, 2009; Silverstein, Kovács, Corry, & Valone, 2000). The relationship between antipsychotic medications and cognitive functioning has been examined (Goldberg et al., 2007; Harvey & Keefe, 2001; Keefe, Bilder, et al., 2007; Mishara & Goldberg, 2004) with research suggesting that medications currently and commonly prescribed to individuals with schizophrenia have either minimally beneficial (Goldberg et al., 2007; Keefe, Sweeney, et al., 2007; Lesh et al., 2015; Meltzer & McGurk, 1999; Spagna et al., 2015) or potentially even slightly deleterious effects on cognitive performance (Élie et al., 2010; Hori et al., 2006; Spohn & Strauss, 1989; Uchida et al., 2009). However, limited work has examined reinforcement learning and visual integration in those off medications. Moreover, limited work has examined the degree to which cognitive impairments are present among unmedicated individuals with chronic schizophrenia using cognitive tasks derived from cognitive neuroscience. The current study, conducted as part of the Cognitive Neuroscience Test Reliability and Clinical applications for Serious mental illness (CNTRaCS) Consortium, examined whether pervasive deficits in cognitive functioning are seen in individuals off as well as on medications across a wide range of cognitive domains.

A number of studies have confirmed the presence of impairments among individuals not taking medications on measures of memory, processing speed and cognitive control (Barch, Carter, MacDonald, Braver, & Cohen, 2003; Braff & Saccuzzo, 1982; Cadenhead et al., 1997). However there is limited work examining individuals with schizophrenia off medications in other cognitive domains impaired in schizophrenia, such as reinforcement learning. For example, research has shown impairments in the ability to learn from reward in medicated schizophrenia patients (Barch et al., 2017; Cicero, Martin, Becker, & Kerns, 2014; Culbreth, Westbrook, Xu, Barch, & Waltz, 2017; Dowd, Frank, Collins, Gold, & Barch, 2016; Gold et al., 2012; Murray et al., 2008; Strauss et al., 2011; Waltz, Frank, Robinson, & Gold, 2007), however less is known about reinforcement learning in unmedicated patients. Reinforcement learning is thought to be critically dependent on the

subcortical dopamine system (Maia, 2009; Montague, Dayan, & Sejnowski, 1996; Schultz, 2007, 2016a, 2016b), which is modulated by many, if not all, of the medications used to treat psychosis (Amato, Vernon, & Papaleo, 2018). There are some hints in the literature that reinforcement learning is disrupted even among unmedicated individuals with schizophrenia (Juckel et al., 2006; Reinen et al., 2016; Schlagenhauf et al., 2014; Stoy et al., 2012), though sample sizes have been small. Thus, additional work is needed in larger samples to assess whether deficits in reinforcement learning are present amongst unmedicated individuals with schizophrenia, and if so, whether the magnitude of such deficits differs from those seen among medicated individuals with schizophrenia.

Visual integration is another domain of cognitive functioning that has consistently shown deficits in schizophrenia (Butler et al., 2013, 2008; Silverstein et al., 2010, 2009, 2015, 2011), with individuals with schizophrenia demonstrating impairments in their ability to integrate visual stimulus elements into a unified visual representation. While the bulk of studies have included medicated individuals with schizophrenia, two studies examining unmedicated patients suggest that these impairments are evident in unmedicated patients as well (Frith, Stevens, Johnstone, Owens, & Crow, 1983; Keri, Kiss, Kelemen, Benedek, & Janka, 2005). Moreover, studies examining the relationship between visual integration and chlorpromazine equivalence suggest that medication is independent from performance (Knight, 1992; Silverstein et al., 2010, 2009; Spencer et al., 2004). However, these studies have relatively small sample sizes and thus additional work is needed to confirm the presence of impairments in visual integration among unmedicated individuals with schizophrenia.

In addition to examining those individuals off medications, type of medication has also been examined. Treatment of schizophrenia often involves medications associated with high anticholinergic burden. Anticholinergic medications can adversely affect learning and memory by blocking the muscarinic M1 acetylcholine receptors (Everitt & Robbins, 1997; Seeger et al., 2004; Tzavara et al., 2003). Indeed research in aging and dementia populations taking anticholinergic medications supports this decrement in memory (Boustani, Campbell, Munger, Maidment, & Fox, 2008; Fox et al., 2011). Studies in schizophrenia suggest a similar pattern, wherein memory and attention deficits appear to worsen as anticholinergic burden increases (Calev, 1984; Eum et al., 2017; Hitri, Craft, Fallon, Sethi, & Sinha, 1987; Minzenberg, Poole, Benton, & Vinogradov, 2004; Perlick, Stastny, Katz, Mayer, & Mattis, 1986; Strauss, Reynolds, Jayaram, & Tune, 1990; Tracy, Monaco, Giovannetti, Abraham, & Josiassen, 2001). In a double blind study, Baker and colleagues (1983) found evidence that patients taken off anticholinergic medications for two weeks showed greater memory performance relative to those who remained on their original medication regiment, though memory performance was reduced relative to controls even among those not taking anticholinergics. Further, Vinogradov (2009) found that serum anticholinergic levels were associated with poorer performance on working memory and verbal learning and that anticholinergic serum level was associated with lower response to cognitive remediation training. Thus, across studies, findings suggest that anticholinergic burden is associated with impaired memory, learning and attention and that medication withdrawal may result in improvements relative to those maintaining their original medication regime. Importantly, the bulk of these studies were limited to learning and attention batteries focused

on neuropsychological tests. To our knowledge, there have been no studies examining relationships between anticholinergic status and reinforcement learning. Further, limited studies have examined this relationship across a battery of cognitive tasks developed from cognitive neuroscience.

The current study had several goals. The primary goal was to examine whether individuals with schizophrenia off medications, as well as those on anti-psychotic medications showed impairments relative to healthy controls across a wide array of cognitive domains in which people with schizophrenia have consistently demonstrated impairment, using behavioral tasks derived from the cognitive neuroscience literature. These domains included: reinforcement learning, visual integration, processing speed, verbal learning, working memory, cognitive control, visual integration and relational encoding and retrieval. As a secondary goal, we also examined associations between cognitive performance and anticholinergic burden.

Method

Participants

Participants were recruited across 5 sites as part of the CNTRaCS Consortium: Maryland Psychiatric Research Center, University of Maryland; University of California, Davis; Rutgers University; University of Minnesota, Twin Cities; and Washington University in St Louis. All participants provided written informed consent to the protocol approved by the local Institutional Review Board.

Participants included 148 medicated individuals with schizophrenia or schizoaffective disorder, 48 unmedicated individuals with schizophrenia or schizoaffective disorder (SZ) and 75 control participants (CON). Exclusion criteria included: 1) history of significant head trauma or neurological disease 2) history of pervasive developmental disorder 3) diagnosis of substance dependence or abuse in the last 6 months 4) score below 6 on the Wechsler Test of Adult Reading (WTAR; (Wechsler, 2001)) 5) failing a drug or alcohol screen administered the day of testing. Additional criteria for the medicated SZ group included no medication changes in the month prior to study participation. The unmedicated group was recruited from the community, and consisted of people meeting inclusion criteria for the patient group. In addition, unmedicated participants were not required to be medication naïve, rather they self-reported that they had not taken medication for at least one month prior to their participation in the study. Additional criteria for CON included: 1) no personal or 1st degree relative with a history of schizophrenia, schizoaffective, or bipolar disorder; 2) no current major depression or dysthymia; and 3) no current psychotropic medication.

Diagnostic status was confirmed using the Structured Clinical Interview for DSM-IV-TR SCID conducted by masters level clinicians. Individuals with SZ were also assessed for general psychiatric symptoms using the Brief Psychiatric Rating Scale (Overall & Gorham, 1962). Negative symptoms were assessed using the Clinical Assessment Interview for Negative Symptoms (CAINS) (Kring, Gur, Blanchard, Horan, & Reise, 2013) which includes a Motivation and Pleasure (MAP) and Expression (EXP) subscale, with higher scores indicating greater impairment. To assess functioning, participants completed the

UCSD-Performance Based Skills Assessment (UPSA) (Harvey, Velligan, & Bellack, 2007) and the Specific Levels of Functioning Scale (SLOF) (Schneider & Struening, 1983) which includes both a self-report and informant report of those close to the participant. Only a subset of participants had informant data collected (Medicated = 100; Unmedicated = 21).

Chlorpromazine equivalency doses were calculated for each participant taking medications using published conversion formulas (Woods, 2003). Anticholinergic load was based on Minzenberg (2004) which includes two scales indexing anticholinergic load: a pharmacological index established from in vitro acetylcholine receptor bindings studies and a clinical index based on expert clinicians' ratings of anticholinergic side effects of medications. Both pharmacological and clinical index were calculated for each participant. Only findings based on the Clinical Index are reported in the current study; however, the two indices were highly correlated (r=.81, p<.001) and the same pattern of findings was observed using either index.

Procedure

As shown in Table 1, participants completed 9 tasks measuring a broad range of cognitive functioning. Each task has been described in detail in earlier reports (Barch et al., 2017; Brandt, 1991; Gold, Carpenter, Randolph, Goldberg, & Weinberger, 1997; Henderson et al., 2012; Keefe et al., 2004; Pizzagalli, Jahn, & O'Shea, 2005; Ragland et al., 2012; Silverstein et al., 2009) and all tasks are described in Table 1. Tasks were administered in a fixed order across participants as presented in Table 1. As the overarching study assessed test-retest reliability, participants completed the same task on multiple visits, with parallel forms used for memory testing. The current study focused all analyses on participants' first session data.

Data Analysis

Primary ANCOVA analyses included group (CON, Unmedicated, Medicated) as a between-subject factor, with age and WTAR score entered as covariates, using post-hoc contrasts for pairwise comparisons. We then conducted analyses in a subset of the groups matched for age, to confirm that age was not confounding the results. Next, we conducted partial correlation analyses examining the relationship between task performance, chlorpromazine equivalency and anticholinergic load, while entering symptom variables of interest (positive symptoms, negative symptoms, and disorganization symptoms) as covariates. Follow-up analyses were conducted within the patient groups (Unmedicated, Medicated) to examine the potential role of BPRS positive symptoms, disorganization symptoms, and negative symptoms. False discovery rate correction was used to correct for multiple comparisons (Benjamini & Hochberg, 1995).

Results

Demographic Information

As shown in Table 2, the unmedicated group was significantly younger than the medicated and CON groups (F(2,271=4.22, p<.05), while the medicated group had a lower WTAR score (F(2,271=17.09, p<.001). Age and WTAR were included as covariates in analyses to account for between group differences. In regard to symptom variables (Table 2), the

unmedicated group reported more positive symptoms relative to the medicated group; however they also displayed less emotional blunting. There were no significant differences between medicated and unmedicated patients in functioning as reported on the SLOF or UPSA.

Implicit and Explicit Reinforcement Learning

IPILT.—As shown in Table 3, we analyzed the IPILT using a repeated-measures ANOVA with Block as a within subject factor and Group (CON, unmedicated, medicated) as a between subject factor. When looking at positivity bias we saw a main effect of Block showing greater bias towards positive response across later blocks. There was no Group or Block x Group interaction. When looking at negative biases on the IPILT-N, we found no Block, Group or Block x Group interaction.

EPILT.—We conducted a repeated-measures ANOVA with Block (4); Condition (Reward, Loss) and Probability (90/10 vs. 80/20) as within subject factors and group (control, unmedicated, medicated) as a between-subjects factor. As shown in Figure 1, we found significant main effects of Block and Probability with better performance across blocks and in the 90% probability condition. A main effect of Group showed that controls performed better than both the unmedicated and medicated patient groups. These main effects were qualified by interactions between Group, Block, and Condition (Table 3). Follow-up analyses indicated that controls performed significantly better across later blocks, which was most pronounced in the Reward conditions wherein the magnitude of difference between the two patient groups and controls was larger (see Figure 1). There were no significant differences between the medicated and unmedicated groups.

Visual Integration

We conducted a repeated measures ANOVA on accuracy with orientational jitter level as a within subject factor and Group (CON, unmedicated, medicated) as a between subject factor (Table 3). We found a main effect of Group wherein medicated patients performed more poorly relative to controls and unmedicated patients ($ps<.05$), while we saw a trend of unmedicated patients performing more poorly than controls ($p=.06$). There was no Jitter Level x Group interaction, which is consistent with prior studies (Silverstein et al., 2009, 2015, 2012).

Processing Speed

As shown in Table 3 and figure 2, an ANOVA with BACS Symbol Coding score as the dependent variable indicated a main effect of Group (CON, medicated, unmedicated) demonstrating higher scores among the controls, followed by the unmedicated SZ group, and the medicated group (all pairwise comparisons significant $p<.05$).

Cognitive Control

An ANOVA with d-prime (d') on the DPX task as the dependent variable (Table 3) indicated a main effect of Group. Post-hoc analyses indicated that both the unmedicated

and medicated groups had significantly lower d' scores relative to controls (p<.001). There was no significant difference between the medicated and unmedicated groups (p=.78).

Working Memory

An ANOVA with LNS total score as the dependent variable indicated a main effect of Group (Table 3). Follow-up analyses showed that CON scored significantly higher than both patient groups (ps<.001), with no significant differences between the medicated and unmedicated groups (p=.13). Examining Run Span Score revealed a significant effect of Group with controls performing significantly better than both patient groups (ps<.05). The unmedicated group performed significantly better than the medicated group (p<.05).

Episodic Memory

For the HVLT (Table 3), we found a significant main effect of Group (CON, unmedicated, medicated) with controls outperforming both patient groups (ps<.05). The unmedicated patients performed significantly better than the medicated group (p<.001).

For the RISE (Table 3), we conducted a repeated-measures ANOVA with encoding condition (Item-Specific Recognition Accuracy, Relational Recognition Accuracy) as a within subject variable and Group as a between subject variable. There was a main effect of condition with participants showing lower performance on the relational recognition task relative to the item recognition task. A significant effect of Group with both medicated and unmedicated groups showed impairments in both conditions relative to controls (ps<.05). There were no significant differences between the medicated and unmedicated groups (p>.20)

Analyses in Age Matched Group

Given that age is known to be related to performance across cognitive domains, we examined whether our findings relating to group differences in unmedicated, medicated and control participants remained when looking at subsets of the participants groups matched for age. We created groups matched on age by sequentially removing older participants in the control and medicated SZ groups until there was less than 1-year difference between groups (F(2,194)=.16, p=85). As shown in Supplemental Table 1, the patient groups still had a lower WTAR score (F(2,194=6.82, p<.005) than controls, however there was no significant difference between the patients groups (p=.61).

When examining the age matched group (CON, unmedicated, medicated), we once again found that CON participants outperformed both the unmedicated and medicated groups across the majority of tasks including processing speed (F(2,190)=15.06, p<.001, η_p^2=.14), cognitive control (F(2,188=6.95, p<.005, η_p^2=.07), letter number sequencing (F(2,190)=12.41, p<.001, η_p^2=.12), original running span (F(2,192)=6.69, p<.05, η_p^2=..07), verbal learning (F(2,191=13.93, p<.001, η_p^2=.13), item-specific encoding (F(2,192)=4.91, p<.01), relational encoding (F(2,192=7.46, p<.005), visual integration (F(2,191=6.45, p<.005, η_p^2=.07) and explicit reinforcement learning (F(2,191=3.31, p<.05, η_p^2=.04). Similar to the analyses in the entire sample, there were no main effects of group when examining implicit reinforcement learning. Age matched medicated participants performed

more poorly than unmedicated participants on the HVLT ($p<.05$), item recognition ($p<.05$) and visual integration ($p<.05$)

Relationship Between Cognitive Performance to Chlorpromazine and Anticholinergic Load Among Medicated Patients

When comparing CPZ dose and task measures (Supplemental Table 2), we found significant relationships that survived multiple comparison correction between CPZ and processing speed (r=−.35, $p<.01$), HVLT (r=−.35, $p<.01$), LNS (r=−.30, $p<.01$), and running span (r=−.30, $ps<.01$) suggesting that higher CPZ load was related to poorer performance across tasks.

As shown in Table 4, we found that HVLT was related to anticholinergic load such that greater anticholinergic load was associated with poorer verbal learning. However, this finding did not remain significant after correcting for multiple comparisons using FDR correction. Further, we conducted an exploratory stepwise analysis entering anticholinergic load in Step 1 and group in Step 2 to predict HVLT, and while the first step was significant (r=.26, r square = .067, p <.005), when group was entered into the model, group was significant ($p<.05$) while anticholinergic load was a trend ($p=.08$).

Examining Potential Symptom Effects within Patient Groups

Finally, we examined whether including positive symptoms, motivation and pleasure, and expressive deficits influenced differences between patient groups (unmedicated and medicated) within each task. While symptom variables were related to some task performance metrics, the overall pattern of group differences remained the same when entering positive and negative symptoms into analyses.

Discussion

The goal of the current study was to examine unmedicated individuals with schizophrenia, as well as those on medications, relative to controls across a range of well-validated cognitive measures. We found that across all but two of the cognitive domains assessed, both unmedicated and medicated patients showed impairments in performance relative to healthy control participants. Further, across every measure other than implicit reinforcement learning, unmedicated patients showed impairments relative to controls, though this was trend level for visual integration.

While the bulk of the literature examining cognitive deficits in schizophrenia has been conducted on medicated samples, current findings suggest that, regardless of medication status, adults with chronic schizophrenia show deficits in tasks assessing processing speed, cognitive control, working memory, relational encoding and retrieval, visual integration and explicit reinforcement learning relative to healthy controls. These findings of cognitive impairment in unmedicated patients are consistent with previous literature showing deficits in working memory, cognitive control, and attention in a young at risk sample (Wood et al., 2003), in first-episode samples (Hutton et al., 1998; Minzenberg et al., 2010; Nejad et al., 2011) and in recent-onset medication-naïve individuals with schizophrenia (Daban et al., 2005; Lussier & Stip, 2001). Our findings of impairments among unmedicated individuals

on an explicit reinforcement learning task is notable, as there have been concerns that medications that block D2 receptors could be creating some of the impairments in this domain. The current findings are consistent with Reinen and colleagues (2016) who found blunted prediction error responses in unmedicated patients relative to controls, suggesting that medication is not driven by antipsychotic medication alone. While not in unmedicated samples, studies examining reinforcement learning in at risk and first episode patients (Chang, Waltz, Gold, Chan, & Chen, 2016; Murray et al., 2008; Waltz et al., 2017), who have presumably a shorter duration of exposure to antipsychotics than chronic samples, also show a pattern of reinforcement deficits relative to controls. However, in a sample of medicated patients Insel and colleagues (2014) found a relationship between dose and lose-shift patterns, suggesting that higher doses was related to greater likelihood to shift choice following negative feedback and in neural response when learning from loss but was not related to learning from reward. Thus, while our findings suggest that unmedicated patients show deficits in reinforcement learning relative to controls, it will be important for future work to look at the relationship of medication and pattern of responding to feedback.

Deficits in visual integration in both medicated and unmedicated groups is notable, as deficits in visual integration have been shown to be related to illness duration (Keane, Paterno, Kastner, & Silverstein, 2016) raising the possibility that medication may be linked to deficits; however only a handful of previous studies have examined the relationship in unmedicated groups. The present findings suggest that unmedicated and medicated individuals show a deficit relative to controls. These findings are consistent with prior research that did not find a relationship in medicated patients between chlorpromazine equivalence and integration (Grove et al., 2018; Keane et al., 2016; Silverstein et al., 2009) and consistent with previous studies showing deficits in unmedicated patients relative to controls (Frith et al., 1983; Keri et al., 2005). Thus, our findings extend previous research suggesting that impairments in visual integration are an aspect of schizophrenia present even among unmedicated individuals with schizophrenia.

Even though we found strong evidence for cognitive impairment among unmedicated individuals with schizophrenia, there were some differences between medicated and unmedicated individuals. Medicated patients had somewhat greater deficits on measures of processing speed, working memory, visual integration and verbal learning relative to unmedicated patients. These patient subgroup differences remained after controlling for symptom domains that differed between groups, including positive and negative symptoms. However, our primary goal was to examine deficits in unmediated individuals and the individuals with schizophrenia were not randomly assigned to medicated versus unmediated groups. While findings in relationship to differences between unmedicated and medicated patient groups are intriguing, it is important to consider a number of variables that may be driving these between group differences and which may also be leading to mixed findings within the literature. Similar to a number of other studies, the present study we took a naturalistic approach to the investigation, recruiting people who had been off antipsychotic medications for at least one month. Given that antipsychotic medication adherence rates are poor with people going on and off medications frequently, our samples are likely representative of the population (Byerly, Nakonezny, & Lescouflair, 2007). However, because they were not randomly assigned to medication groups, there are a number of

group differences which may be important in helping to explain distinctions in cognitive functioning. For example, those taking medications were older, had lower WTAR scores and had more expressive negative symptom deficits. While our results held when controlling for estimated IQ, age, and symptom variables, it is not possible to rule out an influence of these variables out completely. It is also likely that other differences between these groups not captured in the current data may underlie these differential patterns of cognitive performance. For example, it may be the case that those taking antipsychotics in the current study may have had additional comorbid disorders that further impair functioning. While we saw no significant group differences on measures of functioning such as the UPSA or SLOF, there may be other categories of functioning not being fully captured. Nonetheless, the modest difference we saw between medicated and unmedicated individuals needs to be considered in light of the robust deficits we saw in all cognitive domains among unmedicated individuals, other than implicit reinforcement learning, which was not impaired in either medicated or unmedicated patients.

The present study had several limitations. First, as noted above, individuals with schizophrenia were not randomly assigned to medication groups, indeed the majority of studies in this area are not in randomized control trials. Instead participants were under the care of their own mental health providers, thus medication type and dose varied between subjects. While this lends to the generalizability of findings, this also minimizes our ability to examine specific drug related effects. Further, the lack of random assignment to the medication condition led to the medicated and unmedicated groups differing in age. While differences in age were unlikely to have led to null findings between patient groups, they could play a role across tasks in the present study (Braver & Barch, 2002; Hori et al., 2006; McKendrick, Weymouth, & Battista, 2010; Naveh-Benjamin, Hussain, Guez, & Bar-On, 2003; Roudaia, Bennett, & Sekuler, 2008). It will be important for future studies to design studies that address these limitations including randomization and better characterization in naturalistic studies to understand potential differences in the medicated and unmedicated samples that may be leading to differences in findings. Finally, individuals in the unmedicated group were not medication naïve; rather they were required to be off medications for at least 1 month prior to participation. Thus, it could be the case that medication naïve individuals with schizophrenia may show a different pattern of impairments versus those in the present study.

Taken together, the present findings show that individuals with schizophrenia, both unmedicated and medicated, have pervasive deficits across a range of cognitive domains including reinforcement learning, processing speed, cognitive control, working memory, verbal learning, and relational encoding and retrieval. In some domains these deficits appear to be more slightly more pronounced in medicated patients (though still clearly present in unmedicated individuals), particularly on tasks assessing processing speed and verbal learning. However, the fact that the unmedicated individuals showed cognitive impairments in all of the same domains impaired in medicated individuals, even if in some cases to a slightly lesser degree, adds to the body of literature suggesting that cognitive deficits are an enduring aspect of schizophrenia, present in those both on and off antipsychotic medications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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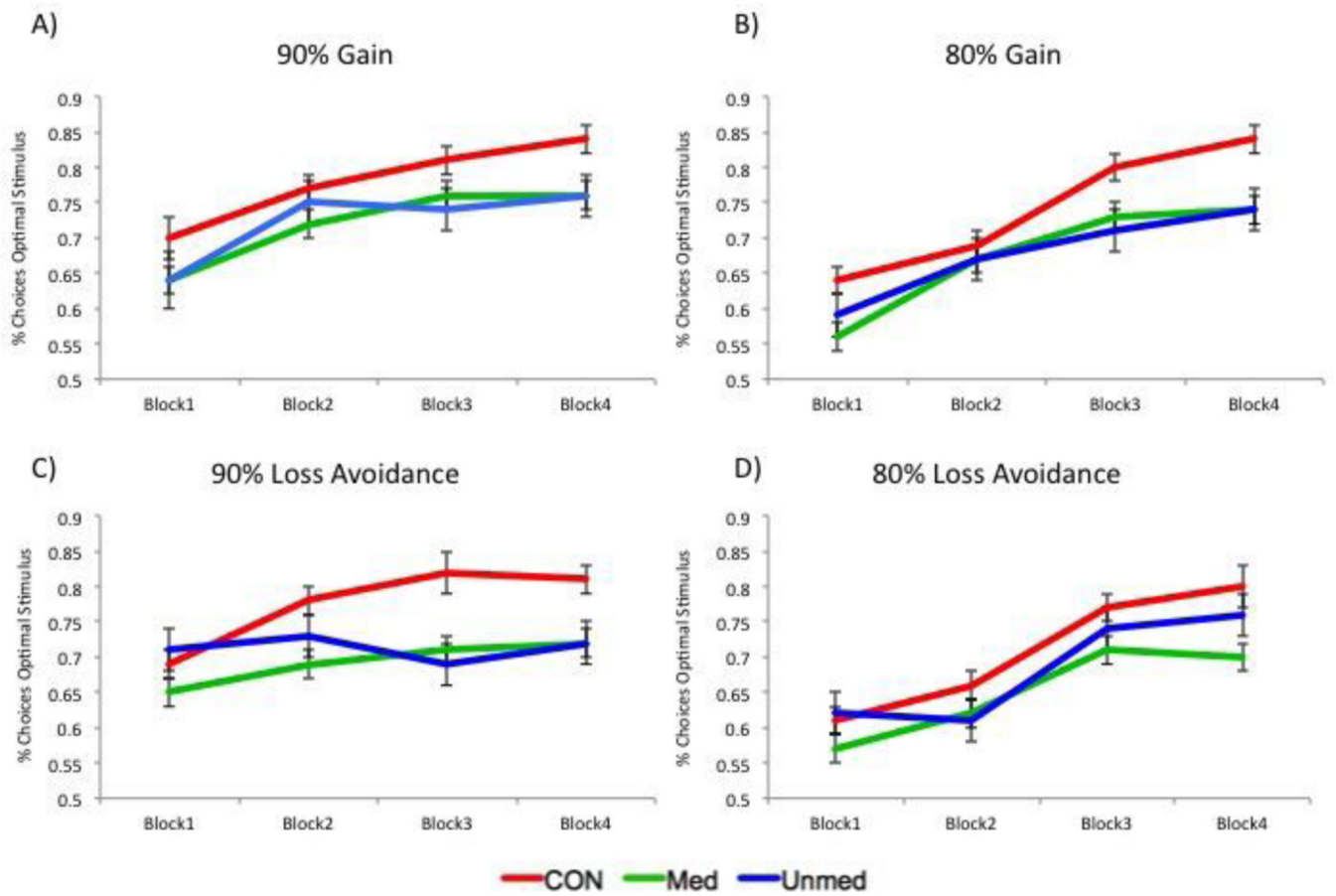
Figure 1.
CON = control; Med = Medicated Schizophrenia; Unmed = Unmedicated Schizophrenia.
Panel A and B display performance on the explicit probabilistic incentive learning task
(EPILT) by group in the 90% and 80% probability gain conditions by group. Panel C and D
display performance on the 90% and 80% probability loss avoidance conditions.
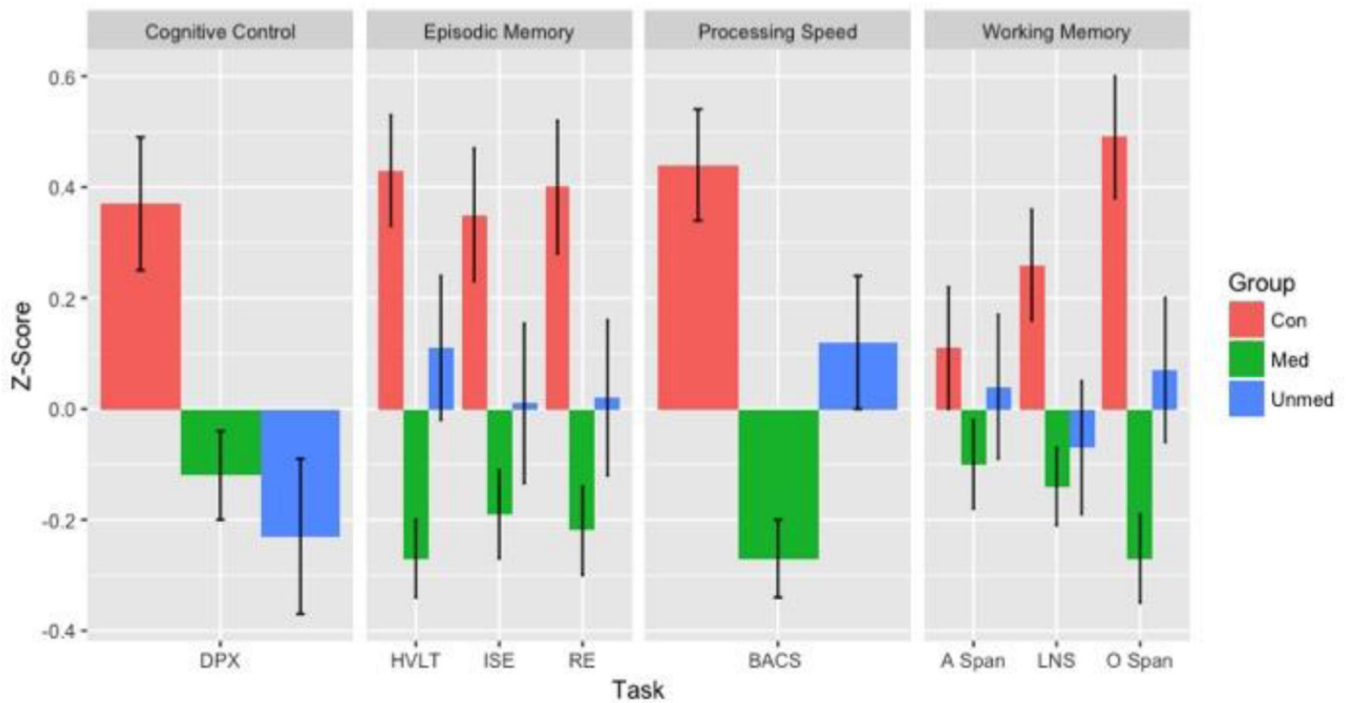
Figure 2.
CON = Control; Med = Medicated Schizophrenia; Unmed = Unmedicated Schizophrenia; DPX = Dot Probe Expectancy; HVLT = Hopkins Verbal Learning Test; ISI = Item Specific Encoding; RE = Relational Encoding; BACS = BACS Symbol Coding; A-Span = Adaptive Running Span; LNS = Letter Number Sequencing; O Span = Original Running Span. Performance on cognitive tasks assessing cognitive control, episodic memory, processing speed, and working memory are presented. Scores were standardized to create z-scores for display purposes.

Table 1.

Task Description in order of administration

Task Name	Reference	Domain	Brief Description	Dependent Variable
Implicit Probabilistic Incentive Learning Task (I-PILT)	Pizzagalli et al., 2005	Reinforcement Learning	Participants are asked to make a judgment regarding the length of a line and are implicitly biased towards selection of a particular stimulus via increased probability for reward or punishment	Response bias $= \frac{1}{2}\log\left(\frac{RICHcorrect * LEANincorrect}{RICHincorrect * LEANcorrect}\right)$
Relational and Item-Specific Encoding (RiSE)	Ragland et al., 2012	Episodic Memory	Participants are asked to encode visual stimuli presented either in pairs to encode them relationally or individual to encode single items. Item and associative recognition tests following encoding are assessed for dependent measure.	Recognition (Hits − False Alarm Rate) for both Relational and Item-Specific Encoding
Explicit Picture Incentive Learning Task (E-PILT)	Gold et al., 2012	Reinforcement Learning	Participants are presented with various picture stimuli that are reinforced at different contingencies (80% or 90%) and asked to learn which images are associated with gain or avoiding loss.	Percentage of pictures accurately selected that were associated with receiving a reward or avoiding loss in the 80% and 90% reinforcement conditions.
Running Span (O-Span)	Broadway & Engel, 2010	Working Memory	Participants are presented with a string of letters and are asked to recall the last X letters.	# of items correctly remembered in their correct position
Hopkins Verbal Learning Test (HVLT)	Brandt et al., 1991	Episodic Memory	Participants are read a list of words and asked to repeat those words across 3 trials.	Total number of correct words recalled across all 3 trials.
BACS Symbol Coding	Keefe et al., 2004	Processing Speed	Participants are asked to quickly write the symbol associated with a given number within 90 s.	T-Score
Letter Number Sequencing (LNS)	Gold et al., 1997	Working Memory	Participants listen to a string of intermixed letters and numbers and then are asked to restate the sequence in numeric and alphabetical order.	T-Score
Dot Probe Expectancy Task (DPX)	Henderson et al., 2012	Cognitive Control	Individuals are asked to discriminate target from non-target dot patterns given a simple rule.	d'-context (AX hits vs. BX false alarms)
Jittered Orientation Visual Integration Task (JOVI)	Silverstein et al., 2011	Visual Integration	Participants are presented with visual stimuli jittered by varying degrees and asked to identify whether the stimulus is pointing to the left or right.	Accuracy

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Table 2:

Subject Demographics

Demographics	Control (N=75)	Medicated (N=148)	Unmedicated (N=48)	Statistic
Gender (% Women)	43%	43%	42%	X^2=.04
Age	35.86 (14.42)	37.93 (10.38)	32.54 (11.06)	F=3.92 * (Med > Unmed)
WTAR Total	39.08 (8.63)	30.17 (10.92)	35.25 (11.69)	F=18.12 ** (CON, Unmed > Med)
Personal Years Education	14.81 (2.27)	12.93 (2.30)	13.54 (2.25)	F=16.63 ** (CON > Med, Unmed)
Parental Years Education	13.67 (3.32)	13.18 (3.40)	13.78 (3.20)	F=1.11
BPRS Positive Symptoms	--	7.74 (4.16)	10.38 (4.77)	t=3.68 ** (Unmed > Med)
BPRS Disorganization	--	5.49 (1.98)	6.71 (3.77)	t=-2.49 ** (Unmed > Med)
CAINS-MAP	--	12.00 (6.43)	13.23 (8.06)	t=1.15
CAINS-EXP	--	3.84 (2.92)	2.68 (3.01)	t=2.31 * (Med > Unmed)
CPZ	--	432.79 (28.85)	--	--
SLOF Total	--	4.23 (.48)	4.23 (.47)	t=-.09
SLOF-Informant Total	--	4.19 (.48)	4.14 (.62)	t=.71
UPSA – Financial	--	39.60 (8.57)	40.69 (7.37)	t=-.75
UPSA - Communication	--	36.50 (8.25)	35.56 (7.89)	t=.68

CON = Control; Unmed = Unmedicated; Med = Medicated

*
$p<.05$

**
$p<.01$

Table 3.

Group differences between Controls, Unmedicated, and Medicated participants.

Task	F-Value	p-value	η_p^2	Direction of Findings
BACS Symbol Coding				
Group	16.94	<.001	.12	CON > Unmed > Med
Dot Probe Expectancy (DPX)				
Group	6.92	.001	.05	CON > Unmed, Med
Letter Number Sequencing (LNS)				
Group	5.70	.004	.04	CON > Unmed, Med
Original Running Span (O-Span)				
Group	6.43	.002	.05	CON > Unmed > Med
Hopkins Verbal Learning Test (HVLT)				
Group	15.61	<.001	.11	CON > Unmed > Med
Jittered Orientation Visual Integration (JOVI)				
Jitter Level	12.77	.001	.05	
Group	7.35	.001	.06	CON > Med
Jitter x Group	.50	.89	.004	--
Implicit Probabilistic Incentive Learning Task Negative (IPILT-N)				
Block	3.57	.03	.01	BL 3 > BL 2 > BL 1
Group	1.08	.34	.009	--
Block x Group	.59	.67	.005	--
Implicit Probabilistic Incentive Learning Task Positive (IPILT-P)				
Block	.13	.72	.001	--
Group	1.01	.37	.008	--
Block x Group	2.37	.06	.02	--
Explicit Probabilistic Incentive Learning Task (EPILT)				
Block	5.43	.02	.04	BL 4 > BL 3 > BL 2 > BL 1
Probability	3.77	.05	.02	90% > 80%
Condition	1.51	.22	.006	--
Group	4.59	.01	.05	CON > Unmed, Med
Block x Group	4.01	.02	.03	See Figure 1

Task	F-Value	p-value	η_p^2	Direction of Findings
Probability x Group	1.16	.32	.01	--
Condition x Group	1.34	.26	.01	--
Block x Condition x Group	5.59	.004	.05	See Figure 1
Relational and Item Specific Encoding (RiSE)				
Encoding Condition	3.77	.05	.02	Item > Relational
Group	7.93	<.001	.06	CON > Unmed, Med
Condition x Group	.88	.42	.007	--

CON = Control; Unmed = Unmedicated; Med = Medicated; BL = Block; Age and WTAR included as covariates in above models.